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ARTICLE

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Use of an Iridium-Catalyzed Redox-Neutral Alcohol-Amine Coupling on Kilogram Scale for the Synthesis of a GlyT1 Inhibitor

Martin A. Berliner,*[,†] Stéphane P. A. Dubant,[‡] Teresa Makowski,[†] Karl Ng,[†] Barbara Sitter,[†] Carrie Wager,[†] and Yinsheng Zhang[†]

[†]Chemical Research and Development, Pharmaceutical Sciences, Pfizer Global Research and Development, Groton Laboratories, 558 Eastern Point Rd, Groton, Connecticut 06340, United States

[‡]Chemical Research and Development, Pharmaceutical Sciences, Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

Supporting Information

ABSTRACT: A recent development for the efficient and environmentally friendly synthesis of aliphatic amines is the transition-metal-catalyzed redox-neutral coupling of an alcohol and an amine, generally referred to as a "borrowing hydrogen" reaction. In this work, we describe the first kilogram-scale application of this technology in the synthesis of PF-03463275, a GlyT1 inhibitor developed for the treatment of schizophrenia. Using $(Cp^*IrCl_2)_2$ the reaction has been optimized to achieve catalyst loadings lower than 0.05 mol % iridium (S/C ≥ 2000) while retaining reasonable reaction times (<24 h). Water and a tertiary amine are essential for high catalytic activity, resulting in dramatically increased reaction rates compared to existing literature protocols. Methods for iridium removal are also described.

INTRODUCTION

The construction of carbon−nitrogen bonds is central to the preparation of bioactive organic molecules. Significant chemical literature is associated with heterocycle synthesis and amine acylation, and more recent and substantial efforts have resulted in development of efficient methods for the transition-metal-catalyzed construction of aryl−nitrogen bonds.[1] In contrast, the transition-metal-catalyzed synthesis of *aliphatic* C−N bonds has received comparatively less attention.[2] These reactions typically proceed via a series of discrete steps involving sequential dehydrogenation of the alcohol (to form a carbonyl compound) followed by imine formation and subsequent reduction (Figure 1). As a result of the action of the catalyst as a hydride shuttle between starting material and product, these processes are typically described in the literature as "borrowing hydrogen" or "hydrogen autotransfer" reactions to reflect the redox-neutral nature of the overall process.

From a process development perspective, application of this chemistry offers several potential advantages over existing techniques (e.g., direct alkylation, reductive amination). In addition to a significant improvement in atom economy (water is the only byproduct of the reaction), the redox-neutral process features operational simplicity and reduced environmental impact through solvent and waste stream reduction. In this report, we describe the optimization and kilogram-scale application of an iridium-catalyzed redox-neutral coupling of an alcohol and a substituted benzylamine as applied to the synthesis of PF-03463275 (**1**), a glycine transporter type 1 (GlyT1) inhibitor that has potential as a therapy for schizophrenia.[3]

The seven-step medicinal chemistry synthesis of PF-03463275 is shown in Scheme 1.[3a] The synthesis starts from *exo*-*N*-benzyl-3-azabicyclo[3.1.0]hexane-6-methanol (**2**),[4] which is converted to the *N*-Boc alcohol **4** via amino alcohol **3**. Swern oxidation of **4** provides aldehyde **5**, which is utilized without purification in a reductive amination with 3-fluoro-4-chlorobenzylamine (**6**) to generate secondary amine **7**. Installation of the amide in **9** is accomplished by coupling with *N*-methylimidazole-4-carboxylic acid (**8**) under typical conditions. After column chromatography, the Boc group in **9** is removed with hydrogen chloride to generate pyrrolidine **10**. In the final step, the *N*-methyl group on the pyrrolidine is introduced using a reductive amination with formaldehyde. Following cleanup by silica gel chromatography, **1** is rendered crystalline by a reslurry in ethyl acetate. Interestingly, all bond-forming steps in the synthesis of **1** from **2**, **6**, and **8** generate new carbon−nitrogen bonds, and no carbon−carbon bonds are formed.[5]

The primary drivers for the development of a new route for the synthesis of **1** focused on operational issues. Most intermediates (**3**, **4**, **5**, **7**, and **9**) are oils, and their salts, while solids, proved to be hygroscopic and unsuitable for handling and storage. We also sought to avoid formaldehyde use in the final step while eliminating the need for protecting groups. We were mindful of the potential difficulties engendered by the presence of unprotected amines in the API and precursors. In practice, this latter concern proved to be the major driver for the selection of chemistry during process development, as many common transformations utilize exogenous amine bases that must be removed during workup. Given this constraint, a step-reordered route to **1** was designed to address many of the existing concerns in the discovery synthesis while incorporating our desired changes (Scheme 2).[6] This modified route is shorter and employs formaldehyde earlier in the process in a telescoped debenzylation/reductive amination reaction to eliminate the need for

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formaldehyde quantification in the API. A new penultimate intermediate, secondary amine **12**, was envisioned to function as an amine donor for acylation of carboxylic acid **8**. This route also introduces the pivotal aliphatic carbon−nitrogen bond construction between alcohol **11** and amine **6**. However, it is important to note that when we committed to this route we had not identified the exact method we wanted to employ for this coupling step.

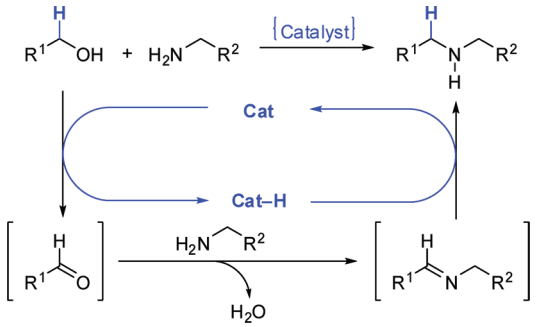
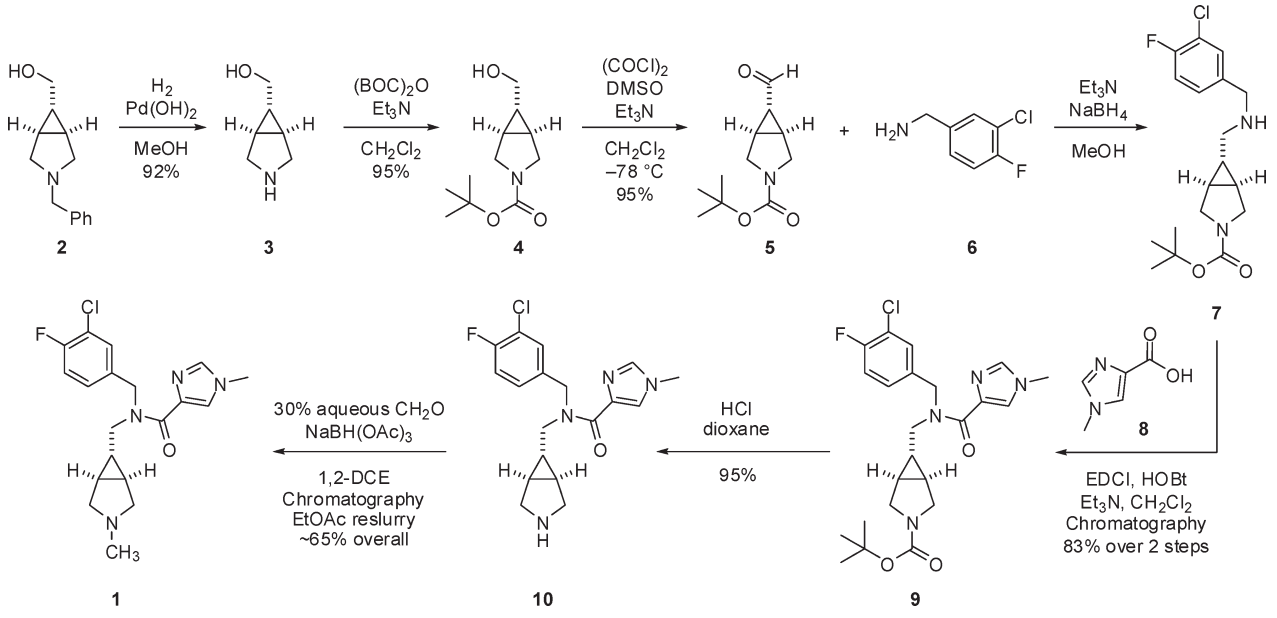


Figure 1. Redox-neutral (borrowing hydrogen, hydrogen autotransfer) aminations.

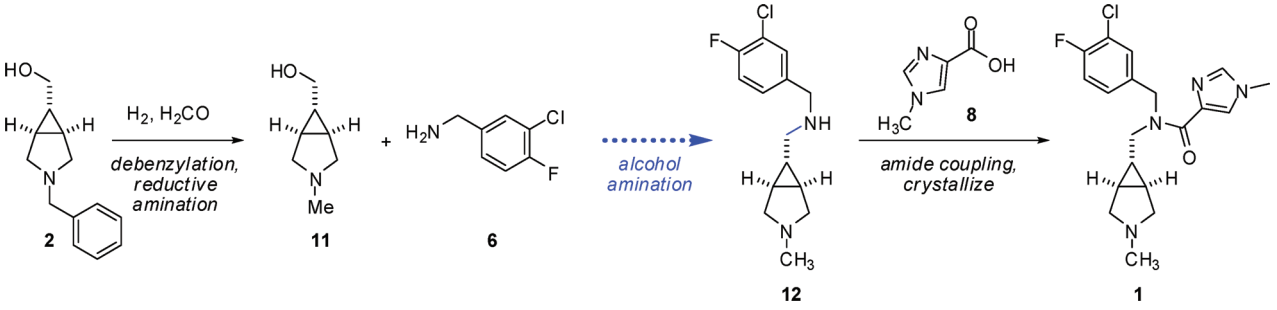
INITIAL PROCESS DEVELOPMENT

Synthesis of Alcohol 11. Debenzylation of **2** is the first step of the medicinal chemistry synthesis and scaled easily without significant modification. The product, amino alcohol **3**, participates in a facile reductive amination with formaldehyde under a hydrogen atmosphere with $Pd(OH)_2/C$ as catalyst.[7] We determined that the two transformations could be conducted sequentially but not simultaneously in the same vessel, as the presence of formaldehyde suppresses the *N*-debenzylation reaction.[8] In the optimized process (Scheme 3), after debenzylation is complete (16 h, 25 °C, 50 psig H_2) a slight excess of aqueous formaldehyde solution (37% w/w) is introduced. Hydrogen is reintroduced to the reactor, and uptake ceases after 4−8 h, at which time **11** is the only observed product. Aqueous dimethylamine is then added and hydrogenation continued. This final step serves to consume any unreacted formaldehyde[9] and results in formation of trimethylamine, which is easily removed by distillation during workup. Water, methanol, and other volatiles are removed by azeotropic distillation with toluene, and alcohol **11** is isolated as a viscous oil by concentration under reduced pressure, typically in yields of approximately 90% for the two steps. While not needing purification before the next step, vacuum distillation of **11** does result in improved color and shelf life. This sequence was

Scheme 1. Medicinal Chemistry Synthesis of PF-03463275



Scheme 2. Planned Process Route



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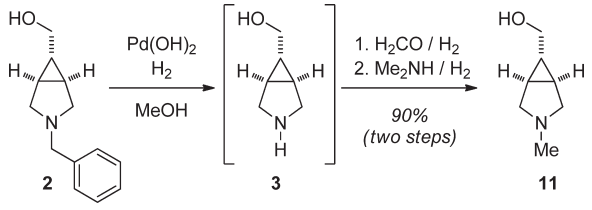
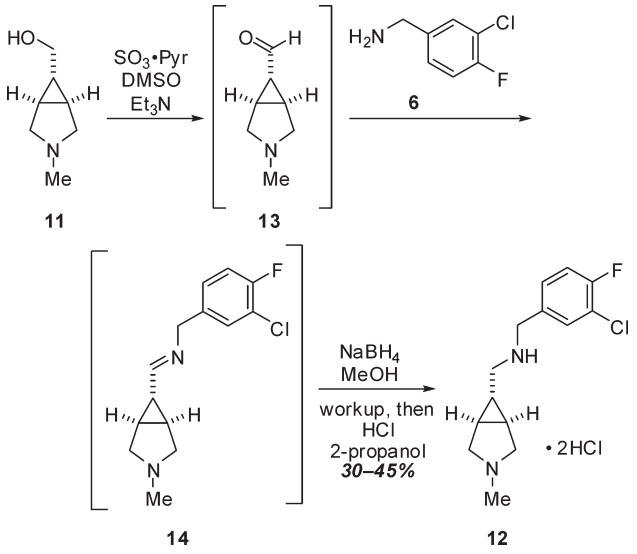
Scheme 3. Final Process Conditions, Synthesis of 11



Scheme 4. Two-Step Synthesis of 12



successfully executed in our kilo lab several times (up to 3 kg scale) and on larger scale (10 kg) by an external vendor.

Implementation of a Two-Step Alcohol Amination. For the first campaign, we chose to implement a two-step oxidation/reductive amination sequence with aldehyde **13** (Scheme 4) as a nonisolated intermediate due to concerns about its stability and water solubility. Activated DMSO oxidations[10] proved superior and of the several variants available, the Corey–Kim,[11] Parikh–Doering,[12] and Swern[13] oxidations were most robust for gram-scale reactions.[14] Of these, Swern and Parikh–Doering processes provided the best reaction impurity profiles in the subsequent step, and on the basis of operational simplicity the Parikh–Doering conditions were chosen for scale-up. Once the oxidation was complete, methanol and amine **6** were added directly to the reaction mixture. Imine formation was observed to be rapid by ^{1}H NMR assay and in situ IR reaction monitoring.[15] Imine **14** was then reduced to the amine by portionwise addition of solid sodium borohydride.[16] After a lengthy work-up,[17] diamine **12** was crystallized as its nonhygroscopic bis(hydrochloride) salt by addition of excess anhydrous HCl in 2-propanol. These crystallization conditions purge most of the process impurities formed in this step (Figure 2), which are primarily the bis-alkylation byproduct **15** and *N*-methylated amines **16** and **17**. The latter two impurities are formed by reduction of methyleneiminium species derived from reaction of DMSO-derived Pummerer degradants[18] with **6** and **12**. The overall yield of **12** in this two-step sequence is 30–45%. A new process was required, and counterintuitively, we uncovered the answer while preparing a small-scale batch of isotopically labeled **1**.

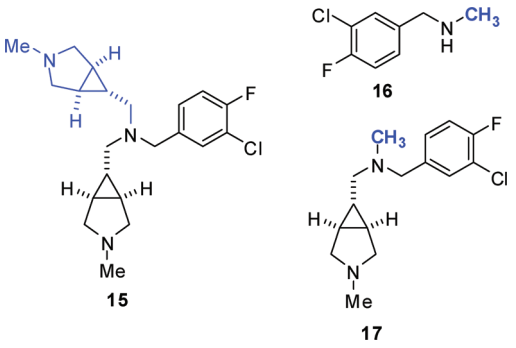
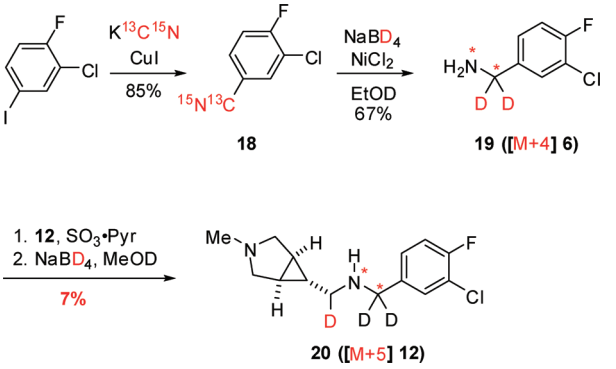


Figure 2. Impurities from the oxidation–reduction process.

Scheme 5. Preparation of Labeled 6 and First Synthesis of [M + 5]-12



DEVELOPMENT OF IR-CATALYZED REDOX-NEUTRAL PROCESS

Initial Application: Synthesis of Stable Isotope-Labeled 12. Because of the presence of a single chlorine atom in **1**, the synthesis of a M + 5 isotopically labeled isomer was required to use as an internal standard for quantitative bioanalytical studies using mass spectrometry. Benzylamine **6** was identified as the preferred site for labeling, and [M + 4]-**6** (**19**) was readily prepared from 1-iodo-3-chloro-4-fluorobenzonitrile via cyanation with in situ prepared [^{13}C/^{15}N]CuCN[19] followed by reduction with nickel boride[20] in d_1-methanol (Scheme 5). Condensation of **19** with alcohol **1** using the conditions described above provided very poor yields of **20** due to the complexity of the process when operating on milligram scale, even when **20** was isolated by column chromatography after work-up.

In 2003, Fujita and Yamaguchi[21] reported that $(Cp^*IrCl_2)_2$ catalyzes the N-alkylation of anilines and primary benzylic amines with primary alcohols at modest temperatures (90–100 °C) with good selectivity for the formation of secondary amines. Direct application of these conditions to the coupling of alcohol **11** and amine **19** proved immediately successful (Scheme 6). Moreover, the condensation was competent under microwave conditions, proceeding to completion in minutes with no significant difference in yield. By pretreating both starting materials with D_2O and MeOD to fully exchange all *N*- and *O*-bound hydrogens for deuterium and taking the resulting D_2O-wet mixture into the reaction, we discovered that an additional deuterium can be introduced in the product. The deuteration occurs selectively on the imine carbon and provides the requisite [M + 5] isomer **20** in

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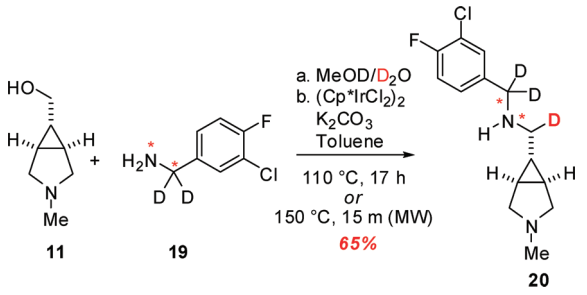
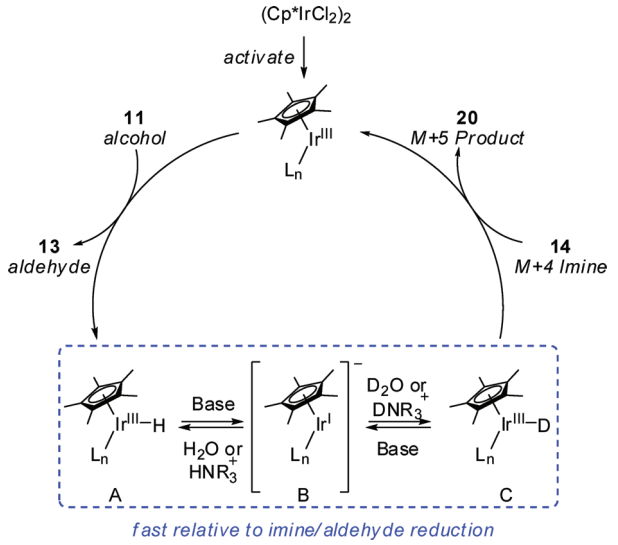
Scheme 6. Preparation of 20 Using Cp*Ir Chemistry



Scheme 7. Possible Mechanism for Deuterium Incorporation



good yield and high isomeric purity. We propose that an equilibrium process that facilitates rapid H-to-D exchange on the metal is responsible for formation of a deuteroidirium(III) species (i.e., **C**), which serves as the reductant (Scheme 7).[22] The source of the deuterium has not been conclusively proven, but likely possibilities include D_2O and/or a *N*-deutero-trialkylammonium species. Notably, in the absence of added D_2O, the reaction between **11** and **19** generates [M + 4]-**20** and little of the desired [M + 5] product. Finally, in the synthesis of **20** we observe no higher-mass isomers, indicating that for this substrate under these reaction conditions the alcohol dehydrogenation and amine reduction are essentially irreversible.

Process Optimization for First Kilogram-Scale Campaigns. The need to resupply nonlabeled **1** led us to implement the Fujita and Yamaguchi chemistry for the synthesis of **12**. Our initial work involved a series of directed screens to evaluate alternative catalysts and identify critical process parameters. In addition to $(Cp^*IrCl_2)_2$, we looked at $(Ru(p\text{-cymene})Cl_2)_2$/DPPF[23] and $Ru(COD)Cl_2$/XantPhos[24] with three different inorganic bases ($NaHCO_3$, K_2CO_3, and Na_2CO_3). Reactions using Ru-based catalysts stalled with large amounts of imine present, while Ir-catalyzed reactions proceeded to completion. Iridium-catalyzed reactions did not proceed to any significant extent with less than 3% iridium present and were more reliable when 5% Ir was employed. The importance of water in the reaction was unexpected, as reactions conducted in the absence of water stalled and produced a yellow inorganic precipitate. The use of 2−3% water on a volume basis prevented this precipitation event and facilitated reactions proceeding to completion, typically in 4−5 h at 100 °C. Additionally, excess **6** in the product mixture proved challenging to purge during crystallization of **12**. Attempts to identify an alternative salt with better crystallization and purification properties failed, so amine **6** was deliberately undercharged (0.9 equiv per equivalent of alcohol **11**) in order to facilitate product isolation and avoid chromatographic purification of the API.[25]

We also looked at purging iridium from the reaction product. Scavenging resins were ineffective at reducing iridium levels in product-containing solutions.[26] Using our existing crystallization process, typical iridium content in isolated **12** bis(hydrochloride) salt was approximately 1000 ppm. This level proved acceptable as a 5- to 10-fold reduction of iridium levels was observed through the remainder of the synthesis.

Unfortunately, this process proved only partially successful when executed on scale (1.5 kg). We observed that the water added to this reaction efficiently distilled as a toluene azeotrope over the first hour of processing and was retained in the reactor vapor trap.[27] This unintentional dehydration (the vapor trap essentially functioned as a Dean−Stark trap) led to the reaction stalling at 70% conversion, and once stalled, return of the water to the reactor did not rescue the process. After work-up, a mixture of HCl salts of **12** and **6** were crystallized from 2-propanol in a 2:1 molar ratio, with an overall yield of 55% calculated on a mass basis. Ineffective washing of the filter cake due to cake cracking resulted in 6000 ppm Ir in isolated **12**, which was higher than expected on the basis of pilot experiments. Finally, the presence of **6** necessitated a chromatographic cleanup of API manufactured from this batch of **12** to meet clinical release specifications.

In preparation for a reload campaign, a series of experiments were conducted to address the issues encountered during the first scale-up of the redox-neutral chemistry. The effect of reactor configuration was addressed by laboratory pilots that verified that semicontinuous return of water to the reaction mixture did not adversely impact the reaction rate and reduced the likelihood for stalled reactions. A more directed effort was made to develop an improved and more reliable iridium purge process by optimizing the crystallization and isolation of **12** as its bis(hydrochoride) salt. The most important factor affecting iridium content in **12** proved to be the protocol and volume of wash solvent of the filter cake. A slight modification of our standard filtration protocol prevented cake cracking,[28] and adding more wash solvent (2-propanol) until the filtrate ran clear and colorless resulted in a 10-fold decrease in iridium levels in **12**. As a side benefit, the increased volume of cake wash also improved the purging of **6** such that it was routinely reduced to levels below 1% in development pilots. Even with these processing changes, the reaction on scale proceeded to only 85% conversion (measured as a ratio of desired product **12** to amine **6**) before stalling. After work-up, crystallization according to the newly optimized conditions provided a 55% yield of **12** bis(hydrochloride) as a white crystalline solid in >98% purity, with <1% benzylamine **6** and 360 ppm iridium.

Robustness Optimization. For the next API campaign, our primary goal was to improve the robustness of the Ir-catalyzed coupling reaction. Small-scale use tests of **6** and **11** in threaded vials went to completion but on 10 g scale in a jacketed reactor under nitrogen the reaction stalled at 60% conversion. Additional experiments in open vessels revealed the consistent nonoptimal

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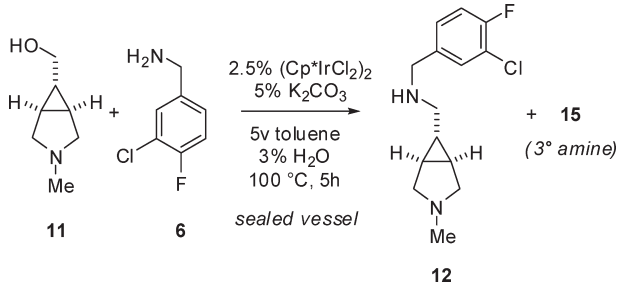
Table 1. Summary of Ir-Catalyzed Reactions (5% Catalyst) in Sealed Reaction Vessels[a]



				ratio[b]			
entry	scale (g)	reactor type	**6** (equiv)	**12**	**6**	**15**	yield (%)[c]
1	1	GL18	0.9	89	2	9	65
2	10	Parr	0.9	81	0	18	60
3	10	Parr	1	88	5	7	74
4	1400	8 L Parr (2 runs)	1	88	5	7	78

[a] All reactions were conducted with 0.025 equiv $(Cp^*IrCl_2)_2$, 0.05 equiv K_2CO_3, 5 vol toluene in a sealed reactor (GL18 threaded capped test tube or 100 mL stirred 316SS Parr reactor) for 4−5 h at 100 °C. [b] Reaction monitoring was via ^{1}H NMR analysis of samples; ratios are reported as molar ratios (see Supporting Information). All reactions proceeded to completion (no detected **11**). [c] Yield is of pure isolated **12** bis(hydrochloride) salt after work-up.

performance of the reaction, with rate variability and catalyst inactivation observed even when obvious water was present in the mixture. We note that in reviewing the available literature on this reaction, including a recently published review by Fujita and co-workers,[29] it was apparent that method development was conducted in sealed vessels without any investigation of the role of water.

A defining experiment in this series serves to illustrate the dramatic improvement in reaction performance observed in sealed reactors. The previous optimal conditions for this process utilized 0.9 equiv amine, which was deliberately undercharged in order to compensate for catalyst deactivation and facilitate isolation of **12** (Table 1, entry 1). When this reaction was run for the first time at 10 g scale in a Parr reactor, **6** and **8** were completely consumed, forming a mixture of **12** and the tertiary amine **15** (ratio 81:18; Table 1, entry 2) from which **12** bis(hydrochloride) was isolated in 60% yield. Improved yields were realized by adjusting reagent stoichiometry to 1:1 (entry 3). An increase in the amount of HCl used to crystallize **12** improved crystallization robustness and reduced the amount of Ir in the isolated salt by ca. 20%. On scale (1.4 kg over 2 runs in a 8 L Hastelloy pressure reactor; entry 4) this reaction went to completion (no detected alcohol **11**) and provided **12** in 78% yield, a dramatic improvement over the previous optimized conditions.

Efficiency Optimization. At the completion of this campaign, we investigated several additional factors that were expected to influence the reaction outcome.[30]

1. Base and Water. A brief survey of base (K_2CO_3 or $NaHCO_3$) and amount of added water (none to 5 equiv) revealed no significant difference in reaction outcome across all combinations, so the use of a saturated aqueous sodium bicarbonate solution (approximately 1 N concentration at 25 °C) was standardized for all future experiments.[31]

Table 2. Product Distribution from Catalyst Optimization Experiments[a]

				composition (molar ratio)[c]		
entry	Ir (mol %)[b]	solvent (vol)	reaction time (h)	**12**	**6**	**15**
1	5	1.0	<5	89	2	9
2	1	1.0	<5	86	5	9
3	0.5	1.0	5	85	7	7
4	0.25	0.2	10	86	6	9
5	0.1	0.2	17	86	5	10
6	0.05	0.2	17	85	6	9
7	0.033	0.2	24	84	7	8
8	0	0.2	24		100	

[a] All reactions were conducted on 1 g scale in capped glass test tubes (5, 1, 0.5 mol % Ir) or 10 g scale in a 100 mL 316SS Parr Reactor using 1 N aqueous $NaHCO_3$ as base at 110 °C for the indicated time. [b] Monomeric iridium. [c] Measured by ^{1}H NMR analysis of a sample of the reaction mixure.

Table 3. Product Distribution from Temperature Optimization Experiments

			composition (molar ratio)		
entry	temp (°C)	reaction time (h)	**12**	**6**	**15**
1	80	72	85	5	8
2	100	24	86	6	8
3	110	17	86	5	10
4	130	<16	86	4	9

2. Catalyst Loading. Catalyst loading was optimized in a series of experiments summarized in Table 2. On gram scale in capped glass test tubes, reactions using 0.5 mol % Ir or greater were complete in 5 h or less (entries 1−3). On this scale, lower catalyst loadings (0.25 mol % Ir or lower) resulted in inconsistent results due to catalyst inactivation. We ascribe this to the very small amounts of catalyst utilized in these experiments (3 mg or less), so screening was continued at 10 g scale. Again, the reaction proved competent as the catalyst charge was reduced a further order of magnitude (entries 4−7) to less than 0.05 mol % Ir (S/C > 2000). Minor and insignificant changes in overall reaction mixture composition accompany catalyst reduction (see Table 2). As a control experiment, a mixture of alcohol **11** and amine **6** were combined with an aqueous solution of $NaHCO_3$ and held in the reactor for 24 h at 110 °C (entry 8) to verify that no reaction occurred. Most notably, no degradation was observed, and upon adding 0.025 mol % $(Cp^*IrCl_2)_2$ (0.05 mol % Ir) and reheating, the reaction proceeded to completion in 17 h (entry 6).

3. Reaction Temperature. Changing the reaction temperature resulted in substantial differences in the rate of the reaction, but no significant differences in reaction composition were observed across the tested temperature range (Table 3).[32]

4. Reaction Solvent. The performance of nonparticipating solvents in the reaction was evaluated under robust conditions (0.25 mol % Ir catalyst, 1 vol solvent). Toluene provided the best result (Table 4, entry 1), with *tert*-butanol (entry 2), a mixture of *tert*-butanol and toluene (entry 3), and isopropyl acetate (entry 4) also giving acceptable results (Table 3). Notably, the use of water

Table 4. Effect of Solvent on Reaction Performance[a]

		composition (molar ratio)			
entry	solvent	**12**	**6**	**15**	**11**
1	toluene	86	6	9	
2	*t*-BuOH	81	7	12	
3	*t*-BuOH/tol (1:1)	83	6	11	
4	*i*-PrOAc	84	8	8	
5	DMAc	76	10	4	10
6	DMSO	75	2	12	11
7	water (no base)	75	13	13	
8	water	64	16	10	10
9	CH_3CN	61	5	34	
10	neat	41	29		29
11	EtOAc	22	32		46
12	2-MeTHF	16	38		46

[a] All reactions were conducted on 1 g scale using 1 vol solvent, 0.25 mol % Ir catalyst, 0.5 mol % aqueous $NaHCO_3$ base at 110 °C for 20−24 h.

Table 5. Iridium in Isolated Samples of 12·2HCl[a]

entry	Ir in reaction (mol %)	Ir in isolated **12**·2HCl (ppm)	Ir reduction (fold)
1	5	300 (300, 360)[a]	140
2	0.25	37	68
3	0.1	16	62
4	0.05	8 (9, 7)[a]	62
5	0.033	4	80

[a] Numbers in parentheses represent valued obtained on batches run on scale (>1 kg **11**). Iridium quantitation by ICP/MS.

alone as solvent was inferior, although catalytic activity is improved in the absence of base (entries 7, 8).[33] Similar results were obtained using polar aprotic solvents (entries 5, 6). Poor catalyst activity was observed in ethyl acetate (entry 11) and 2-methyltetrahydrofuran (entry 12) and in the absence of solvent (entry 10). With the exception of the reaction in ethyl acetate, in which appreciable ester hydrolysis occurred, all reactions were clean (i.e., no degradation products were apparent), highlighting the wide range of functional group compatibility exhibited by this catalytic system.

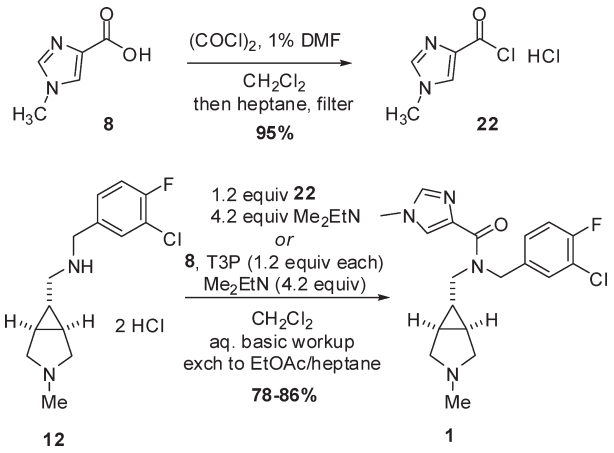
5. Work-Up and Isolation Modifications. By reducing catalyst charge to less than 0.1 mol % Ir, the amount of carbonate base added to the reaction was reduced to very low levels and did not need to be removed via aqueous extraction prior to work-up. Consequently, the work-up of this reaction was eliminated, and the crude reaction mixture directly exchanged into 2-propanol via azeotropic displacement of toluene at reduced pressure prior to salt formation. Filter cake wash volumes were maintained as they serve a dual role of reducing iridium and purging of **6** in the product to below 1%. Iridium reduction ranged between 60- and 140-fold during crystallization (Table 5) and generated **12** bis(hydrochloride) salt that did not require additional iridium mitigation in subsequent operations.

Performance of Optimized Conditions on Scale. After these efforts were complete, two additional campaigns were conducted (Table 6). The first employed the optimized conditions described above (0.05 mol % Ir, aqueous $NaHCO_3$ solution, 0.2 L/kg toluene, 110 °C). Due to decreased solvent use, the reaction was conducted on larger scale (2.4 kg **11**) in a single run in a 8 L Hastelloy pressure reactor. Reaction performance was slower on scale; after 18 h the reaction was only 70% complete. Facility scheduling constraints necessitated that we add an additional 0.0125 mol % iridium to drive the reaction to completion, which was reached after 40 h (<2% **11** remaining). The rate discrepancy between pilots and the scale-up was subsequently determined to be due to an initial temperature overshoot in the laboratory reactor that resulted in an accelerated initial reaction rate and faster overall reaction performance. For the second campaign, a slight initial increase in catalyst loading and reaction temperature (to 115 °C) avoided the necessity of adding additional catalyst, affording complete conversion (<0.5% **11** remaining) in 36 h.

Table 6. Low-Catalyst Scale-Up Runs

entry	**11** (kg)	Ir used (mol %)	**12** (%)	**6** (%)	**15** (%)	**11** (%)	yield (**12**·2HCl)	Ir (ppm)
1	2.4	0.0625	80.6	8.4	9.3	1.7	4.81 kg (76%)	9.2
2	2.4	0.0750	83.6	8.1	8.0	0.3	4.54 kg (69%)	6.9

Scheme 8. Synthesis of 1



FINAL ACYLATION AND IRIDIUM CONTROL

Two variations of the API synthesis have been implemented on scale. We initially conducted a two-step process involving acylation of **12** with acid chloride **22**, which was prepared from **8** under typical conditions (Scheme 8). For the acylation, dichloromethane is a preferred solvent,[34] and the reaction is rapid using excess dimethylethylamine (DMEA) as base.[35] This base was chosen strictly on the basis of its low boiling point (38 °C) rather than on any intrinsic difference in reactivity between DMEA and more commonly used tertiary amine bases. As a result of the basicity of the API, the work-up of this reaction required full neutralization with aqueous base[36] prior to a water wash to prevent extraction of salts of **1** into the aqueous phase. If necessary, an iridium scavenging operation was conducted at this stage. Solvent displacement with ethyl acetate facilitated removal of CH_2Cl_2 and DMEA, and after concentration of the mixture to ~3 L/kg, **1** crystallized upon cooling as white needles. Heptane was added as antisolvent prior to isolation to increase yield. In some campaigns we observed small amounts of off-colored

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Table 7. Removal of Iridium from 1 Using Scavenging Agents[a]

entry	resin name	Ir amount (ppm)	removal of Ir (%)	main product recovery (%)
1	Ecosorb C908	86	82	93
2	Ecosorb C941	65	86	91
3	Norit CA1 (B)	104	78	90
4	Darco KBB (B)	60	87	92
5	Norit CA1	99	79	93
6	CUNO SASS R55	64	87	95
7	Darco KB-B 278106	83	83	91
8	Biotage AC 2604-1	81	83	90

[a] The batch of **1** used for this study had ~475 ppm Ir. Iridium quantitation by ICP/MS.

waxy solids in the filter cake; these proved to be a complex mixture containing **1** and several other API-related components.[37] A repeat of the reaction work-up proved sufficient to purge these materials and generate clinical grade API.

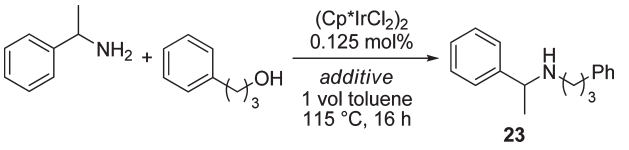
Acid chloride **22** demonstrates nonideal storage and handling qualities, and its synthesis, while straightforward, employs DMF with oxalyl chloride, which can form *N*,*N*-dimethylcarbamoyl chloride (DMCC), a suspected human carcinogen.[38] While not a significant issue in this process due to the aqueous base work-up after the acylation, implementation of a direct coupling protocol between **12** and acid **8** promised to improve the overall efficiency of the process and reduce overall solvent use. We elected to implement a T3P-mediated process primarily because of the water solubility of its degradants (propanephosphonic acid salts) upon quenching and work-up with aqueous base. This reaction also performed best in dichloromethane, and work-up and product isolation were conducted as before, obtaining similar overall yields and product quality.

Methods for Iridium Control. Prior to development of the low-catalyst amine coupling reaction, we needed a way to control iridium at the API stage to meet product quality guidelines. A screen of several dozen scavenging agents and carbons quickly revealed that few proved effective at iridium sequestration without incurring significant loss of material (Table 7).[39] For all experiments, 100 wt % of scavenger was employed in organic solvent for 14−24 h at ambient temperature. Darco KBB (entry 4) was selected for use in subsequent scale-up efforts on the basis of recovery efficiency and low cost. In practice, we observed typical iridium reductions of ~85% (for example, 360 ppm Ir in **12** was reduced to 60 ppm Ir in crystallized API).

DISCUSSION AND CONCLUSIONS

We have discovered that several factors are essential for ensuring robust catalyst performance. The most important is that use of a tertiary amine base appears to be necessary to realize improved turnover. This effect was briefly explored on a model system by evaluating the reaction between phenethylamine and 3-phenyl-1-propanol, which has been reported to be quite sluggish under standard conditions in the absence of any additives.[33a] Significant improvement in overall reaction performance was obtained when any one of several common tertiary amine bases were added in substoichiometric (5 mol % as a solution in 1 vol toluene) or stoichiometric (100 mol %; reaction solvent) quantities (Table 8). Unsatisfactory results were obtained when triethylamine and

Table 8. Effect of Added Tertiary Amine Base on Model Reaction Performance[a]



23

entry	additive (amount)	conversion (%)
1	none	20
2	1 N $NaHCO_3$ (0.25 mol %)	20
3	1 N NaOH (1 mol %)	0
4	30% w/w Bu_4NOH in water (1 mol %)	0
5	*N*-methylmorpholine (1 equiv)	92
6	*N*-methylpiperidine (1 equiv)	94
7	*N*-methylpyrrolidine (1 equiv)	94
8	*N*-methylpyrrolidine (5 mol %)	95
9	1,4-dimethylpiperizine (5 mol %)	95
10	TMEDA (5 mol %)	94
11	DABCO (5 mol %)	93
12	*N*-methylpyrrolidine (1 equiv)[b]	87 (65)[c]

[a] Except for entry 12, all reactions were conducted in sealed test tubes on 1 g (alcohol) scale at 115 °C for 16 h. Reactions with 1 equiv additive were run without solvent; others employed 1 vol toluene. Conversion is measured as the ratio of reaction product(s) to starting amine. [b] 10 g scale with 0.05 mol % $(Cp^*IrCl_2)_2$ at 130 °C for 40 h. The reaction stalled at 87% conversion (TON = 870). See the Supporting Information for analytical details. [c] Isolated yield of **23** monohydrochloride salt; see the Experimental Section for the procedure.

N-ethylpyrrolidine were utilized due to formation of significant amounts of *N*-ethylated byproducts from competitive amine cross-coupling processes.[40,41] In general, bases that do not readily form enamines upon dehydrogenation appear to be preferred. Inorganic carbonate bases seem to be unnecessary but not deleterious, but hydroxides kill catalytic activity (entries 2 and 3).[42] A larger-scale run (entry 12) with stoichiometric *N*-methylpyrrolidine as solvent proceeded to partial conversion (catalyst TON = 870, 65% isolated yield), indicating that further optimization of this reaction is required to achieve optimal (>2000 TONs) catalyst performance. These reactions appear to perform better above the azeotropic boiling point of the solvent/water mixture, and therefore the chemistry is better suited for sealed vessels or for flow equipment where the temperature can be significantly elevated above the boiling point. Water may also play a role in facilitating catalyst turnover but we have not yet quantified its influence. Finally, the distribution of products (starting materials, the desired product and overalkylated products) is dependent on starting material steric demands and stoichiometry, is influenced by the reaction solvent and additives, and does not appear to be overly influenced by reaction temperature. Because of this, each substrate would need to be optimized individually.

In conclusion, the optimized conditions for the iridium-catalyzed coupling reaction between alcohol **11** and amine **6** as described and implemented above represent a significant improvement over existing literature examples, in which a catalyst loading of 1 mol % or greater is utilized. Our initial experience optimizing and scaling this reaction was decidedly mixed due to poor reproducibility and high catalyst loading. However, we were

able to successfully address these issues in subsequent campaigns. In doing so, we have identified critical process parameters that allowed us to achieve a 20- to 100-fold decrease in catalyst loading over the existing best-in-class procedures for the coupling of similar compounds.[43] While the role of water and the amine base in this reaction have not been fully quantified, we have demonstrated that their presence is critical to achieving efficient and robust catalyst performance on both small and large scale. The finding that the intermediate acidic iridium hydride species can be utilized for isotopic enrichment of substrates through H-D exchange with D_2O was unexpected. The significant operational and environmental advantages of this process over traditional oxidation-reductive amination sequences should serve to encourage chemists faced with similar bond-forming challenges to investigate this technology. Finally, experiments to further elucidate the reaction mechanism and develop generalized conditions for high turnover solution-phase reactions in batch- and flow-mode are in progress and will be reported in due course.

EXPERIMENTAL SECTION

((1*R*,5*S*,6*r*)-3-Methyl-3-azabicyclo[3.1.0]hexan-6-yl)methanol (11). An inerted 30 L Hastelloy pressure reactor was charged with $Pd(OH)_2$ (20% Pd content, 50% wet, 275 g), methanol (20 L, 7.2 L/kg) and ((1*R*,5*S*,6*r*)-3-benzyl-3-azabicyclo[3.1.0]hexan-6-yl)methanol (**2**, 2.75 kg, 13.5 mol, 1 equiv). After three purge/vent cycles, the mixture was warmed to 30 °C, and the reactor was pressurized with hydrogen gas (50 psig). When hydrogen uptake ceased (approx 16 h), the reactor was purged, and a solution of formaldehyde in water (37% w/w, 1.32 kg, 16.2 mol, 1.2 equiv) was charged in one portion. The reactor was purged and repressurized with hydrogen gas at 50 psig, and the mixture was held at 30 °C for 8 h. Upon cessation of hydrogen uptake (8 h), the reactor was purged, and dimethylamine in water (40% w/w, 0.61 kg, 5.4 mol, 0.4 equiv) was charged in one portion. Hydrogenation was continued at 30 °C and 50 psig for another 4−8 h. The resulting reaction mixture was filtered to remove catalyst, and the solvent was displaced from methanol into toluene via a constant-volume distillation under reduced pressure, removing methanol, water, dimethylamine, and trimethylamine. The mixture was filtered to remove residual colloidal palladium residues, and after additional concentration, the resulting light yellow toluene solution of **11** was removed from the reactor. A gravimetric assay of the solution indicated a total of 1.55 kg of **11** was present (12.2 mol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (d, J = 7.2 Hz, 2 H) 3.04 (br. s., 1 H) 2.97 (d, J = 9.0 Hz, 2 H) 2.26 (m, 2 H) 2.23 (s, 3 H) 1.42 (tt, J = 7.2, 3.4 Hz, 1 H), 1.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.7, 57.0 (2C), 41.5, 22.5, 21.5 (2C). IR (thin film, cm^{-1}): 3316 (br), 2889, 2785, 1450, 1348, 1222, 1146, 1033, 991, 843. HRMS (ES+): calcd for $C_7H_{14}NO$ (M + H) 128.1075, found 128.1074.

***N*-(3-Chloro-4-fluorobenzyl)-1-((1*R*,5*S*,6*s*)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)methanamine Bis(hydrochloride) (12).** A 8 L Hastelloy pressure reactor was charged with alcohol **11** (2.4 kg, 18.6 mol, 1 equiv), 3-chloro-4-fluorobenzylamine (2.97 kg, 18.6 mol, 1 equiv), pentamethylcyclopentadienyliridium(III) chloride dimer (3.70 g, 4.6 mmol, 0.00025 equiv), a 1 N aqueous sodium bicarbonate solution (9.2 mL, 9.2 mmol, 0.0005 equiv), and toluene (470 mL, 0.2 L/kg). The reactor was purged with nitrogen and then sealed and heated to an internal temperature of 110 °C and held for 24 h. The maximum internal pressure during the reaction was 25 psig. At the end of this time period the reactor contents were cooled and sampled; the reaction was 70% complete. An additional charge of catalyst (1.42 g, 1.8 mmol, 0.0000625 equiv) and aqueous sodium bicarbonate solution (3.5 mL) were added to the mixture, which was purged and heated to 110 °C for 16 h. The contents were cooled and sampled; the reaction was complete (<2% alcohol **11** remaining).[44] The mixture was then transferred to a 100 L glass-lined reactor, diluted with 7.2 L 2-propanol, and distilled under reduced pressure (0.2 bar). When the pot volume reached ∼7 L, 2-propanol (7.2 L each) was added, and distillation was continued, again reducing the volume to ∼7 L. After a second dilution with 2-propanol (7.2 L), the mixture was concentrated to 7 L, cooled to ambient temperature, and transferred slowly into a reactor containing a preheated (50 °C) solution of 5 N HCl in 2-propanol (9.31 kg, 2.75 equiv). Once the freebase had been added, the resulting slurry was cooled to ambient temperature at 10 °C/h and granulated for 4 h. The product was isolated by filtration, and care was taken to stop the filtration immediately before the cake was exposed to nitrogen. The filtercake was then washed with 2-propanol (72 L), and the resulting product dried to constant mass in a vacuum oven (50 °C, 0.05 bar). A total of 4.81 kg (14.1 mol, 76% yield) of **12** was isolated as a free-flowing, nonhygroscopic white crystalline powder. Mp 232 °C. The spectroscopic properties of the salt are nonideal, and therefore a sample was freebased for characterization. ^{1}H NMR (400 MHz, $CDCl_3$, freebase): δ 7.34 (dd, J = 2.1, J_{HF} = 7.1 Hz, 1 H), 7.13 (ddd, J = 2.2, 8.3 Hz, J_{HF} = 4.8 Hz, 1 H), 7.01 (app t, J = 8.8 Hz, J_{HF} = 8.8 Hz, 1 H), 3.71 (s, 2 H), 2.95 (d, J = 8.8 Hz, 2 H), 2.40 (d, J = 6.8 Hz, 2 H), 2.25 (s, 3 H), 2.28 − 2.22 (m, 2H), 1.30 (tt, J = 3.3, 6.8 Hz, 1 H), 1.18 - 1.13 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$, freebase): δ 157.0 (d, J_{CF} = 247 Hz), 137.7 (d, J_{CF} = 3.7 Hz), 130.0, 127.5 (d, J_{CF} = 7.2 Hz), 120.7 (d, J_{CF} = 17.5 Hz), 116.3 (d, J_{CF} = 20.4 Hz), 57.1, 52.27, 51.5, 41.4, 22.3, 20.2. ^{19}F NMR (376 MHz, $CDCl_3$, freebase): δ −119 (m, 1F). IR (thin film, cm^{-1}): 2886, 2776, 1499, 1449, 1406, 1346, 1247, 1059, 846, 818. HRMS (ES+): calcd for $C_{14}H_{19}ClFN_2$ (M + H) 268.1221, found 269.1221.

1-Methyl-1*H*-imidazole-4-carbonyl Chloride Hydrochloride (22). A 75 L glass-lined reactor was charged with 1-methyl-1*H*-imidazole-4-carboxylic acid (1.2 kg, 9.52 mol, 1 equiv), dichloromethane (12 L, 10 volumes), and DMF (12 mL, 1 vol/vol%). The resulting slurry was cooled to 5 °C, and oxalyl choride (1.33 kg, 1.10 equiv) was added over 45 min while maintaining the temperature between 0 and 10 °C. The reaction mixture was held for 2 h at 5 °C, warmed to 25 °C, and held for an additional 8 h. Heptane (12 L, 10 volumes) was added, and the slurry granulated 15 min. The product was isolated by filtration, washed with heptane (12 L, 10 volumes), and dried under a nitrogen stream for at least 6 h. A total of 1.62 kg (94% yield) of acid chloride HCl salt **22** was isolated as a fluffy off-white hygroscopic solid and was stored tightly sealed and protected from moisture to prevent degradation. ^{1}H NMR (DMSO-d_6): δ 14.6 (br s, 1H), 9.16 (s, 1H), 8.30 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 159.0, 138.5, 127.6, 125.1, 35.8.

PF-03463275 (1), Acid Chloride Route, with Carbon Treatment To Reduce Iridium. A 100 L glass-lined reactor was charged with **12** bis(hydrochloride) salt (2.44 kg, 7.14 mol, 1 equiv, 360 ppm Ir), acid chloride **22** (1.62 kg, 8.57 mol, 1.2 equiv), and dichloromethane (24.4 L, 10 volumes). The resulting slurry was cooled to 5 °C, and *N*,*N*-dimethylethylamine (2.19 kg, 3.25 L, 30 mol, 4.2 equiv) was added at a rate to maintain the internal temperature below 10 °C. The resulting thin suspension was

warmed to 25 °C and held for 30 min, at which time the acylation was complete (<1% **12** remaining). A solution of sodium carbonate (3.18 kg, 30 mol, 4.2 equiv) in water (29 L) was added in one portion, and the layers were mixed for at least 30 min, allowed to settle, and split. The lower organic phase was returned to the reactor and washed with water (11 L). The layers were again split. The lower organic phase was returned to the reactor, a slurry of Darco KBB (1.22 kg, 50 wt %) in dichloromethane (5 L) was added to the solution of product, and the slurry was mixed for 4 h. This mixture was filtered through a polishing filter into a speck-free reactor, and the filter was washed with dichloromethane (10 L). This product-rich solution was then displaced into ethyl acetate by azeotropic distillation at atmospheric pressure, reaching a final volume of 8 L. At this point the solution was cooled to 40−42 °C and held to crystallize **1**. The slurry was then cooled to 30 °C, and heptane (20 L) was added, and further cooled to 15 °C. After granulating for 3 h, the product was isolated by filtration, washed with 25 L of a 4:1 heptane/ethyl acetate mixture, and dried under vacuum. A total of 2.14 kg of **1** was isolated (79% yield). Mp 125 °C. ^{1}H NMR (600 MHz, 373 K, DMSO-d_6): δ 7.59 (d, J = 2 Hz, 1H), 7.54 (bs, 1H), 7.44 (d, J = 6.9 Hz, 1H), 7.27 (m, 1H), 7.26 (d, J = 2 Hz, 1H), 4.98 (br s, 2H), 3.69 (s, 3H), 3.57 (br s, 2H), 2.74 (d, J = 8.7 Hz, 2H), 2.19 (m, 2H), 2.17 (s, 3H), 1.31 (tt, J = 3, 7 Hz, 1H), 1.26 (m, 2H). ^{13}C NMR (150 MHz, 373 K, DMSO-d_6): δ 164.8, 157.6 (d, JCF = 246 Hz), 138.7, 138.6, 138.4 (d, J_{CF} = 4 Hz), 130.7, 129.2 (d, J_{CF} = 7 Hz), 127.5, 120.6 (d, J_{CF} = 18 Hz), 117.7 (d, J_{CF} = 21 Hz), 57.8 (2C), 50.5, 50.0, 41.8, 34.3, 23.5 (2C). Anal. Calcd for $C_{19}H_{22}ClFN_4O$: C, 60.55; H, 5.88; Cl, 9.41; F, 5.04; N, 14.87. Found: C, 60.42; H, 5.97; N, 14.79. HRMS (ES+): calcd for $C_{19}H_{23}ClFN_4O$ (M + H) 377.1544, found 377.1539.

PF-03463275 (1), Carboxylic Acid Route with T3P and No Carbon Treatment. A 200 L glass-lined reactor was charged with **12** bis(hydrochloride) salt (4.54 kg, 13.3 mol, 1 equiv), 1-methyl-1*H*-imidazole-4-carboxylic acid (1.76 kg, 13.9 mol, 1.05 equiv), *N*,*N*-dimethylethylamine (4.13 kg, 6.1 L, 56.5 mol, 4.25 equiv), and dichloromethane (23 L, 5 volumes). The resulting slurry was cooled to 10 °C, and T3P (50% solution in ethyl acetate, 10.6 kg, 9.9 L, 16.6 mol, 1.25 equiv) was added at a rate to maintain the internal temperature below 10 °C. The resulting thin suspension was held for 1 h at 10 °C and then warmed to 25 °C and held for 8 h, at which time the reaction was complete (<1% **12** remaining). A solution of sodium carbonate (5.91 kg, 56 mol, 4.2 equiv) in water (51 L) was added in one portion, and the layers were mixed for 60 min, allowed to settle, and split. The upper organic phase was washed twice with water (23 L each wash). The layers invert for the water washes. After the last water wash, the lower organic phase was filtered through a polishing filter into a speck-free 100 L reactor. This product-rich solution was then displaced into ethyl acetate by azeotropic distillation at atmospheric pressure, reaching a final volume of 18 L. At this point the solution was cooled to 40−42 °C and held to crystallize **1**. The slurry was then cooled to 20 °C, and heptane (36 L) was added. After granulating for 3 h, the product was isolated by filtration, washed with 36 L of a 3:1 heptane/ethyl acetate mixture, and dried under vacuum. A total of 4.34 kg of **1** was isolated (87% yield).

3-Chloro-4-fluoro(*cyano*-^{13}C,^{15}N)benzonitrile (18). 3-Chloro-4-fluoro-1-iodobenzene (3.09 g, 11.7 mmol) was combined with (^{13}C,^{15}N)-copper(I) cyanide (10.9 g, 10.9 mmol) in DMF. The mixture was heated to 110 °C for 4 h and then cooled to ambient temperature. Ethyl acetate (30 mL) and water (30 mL) were added, and the mixture was filtered through Celite. The resulting filtrate was extracted with brine and water (twice), dried with $MgSO_4$, and concentrated to give 1.83 g (74%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (m, 1H), 7.52 (m, 1H), 7.30 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 160.8 (d, 1C), 134.7 (s, 1C), 132.5 (d, 1C), 122.8 (d, 1C), 117.9 (d, 1C), 116.8 (s, 1C, ^{13}CN), 109.5 (d,1C). LC-MS (ES+): m/z 158 (M + H)

1-(3-Chloro-4-fluorophenyl)(^{13}C,^{2}H$_2$)methan(^{15}N)amine (19). Nitrile **18** (0.85 g, 5.4 mmol, 1 equiv) was mixed with $NiCl_2$ (1.2 g, 9.2 mmol, 1.7 equiv) in MeOD (35 mL). $NaBD_4$ (1.55 g, 37 mmol) was added portionwise over 30 min, and then the reaction mixture was allowed to warm to ambient temperature and held for 1.5 h. The mixture was then diluted with methanol (10 mL) and filtered through Celite. The filtrate was partitioned between ethyl acetate (30 mL) and water, and the organic phase was then filtered again through Celite to give a clear, colorless solution. This material was dried with $MgSO_4$ and concentrated, and the residue was purified by flash chromatography on silica gel (EtOAc to 6% MeOH/EtOAc) to provide 0.5 g (57%) of **19** as a clear, colorless oil. LC-MS (ES+) m/z 164.2, 146.1 (M − NH_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 1H), 7.15(m, 1H), 7.01(m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.5 (d, 1C), 140.2 (s, 1C), 128.7 (s, 1C), 127.4 (s, 1C), 120.8 (s, 1C), 116.5 (d, 1C), 45.8 (d, 1C, $^{13}CD_2NH_2$).

1-(3-Chloro-4-fluorophenyl)-*N*-{[(1*R*,5*S*,6*s*)-3-methyl-3-azabicyclo[3.1.0]hex-6-yl](^{2}H$_1$)methyl}(^{13}C,^{2}H$_2$)methan(^{15}N)amine (21). Alcohol **11** (160 mg, 1.26 mmol, 1.03 equiv) was mixed with **19** (200 mg, 1.22 mmol, 1 equiv) in MeOD (5 mL) and D_2O (1 mL), and the resulting solution was stirred for 15 h. The solvent was evaporated, and the residue was redissolved and concentrated from MeOH (5 mL) and D_2O (1 mL) three more times to fully deuterate the amine and alcohol. The residue was dissolved in d_8-toluene (2 mL), and K_2CO_3 (20 mg, 12 mol %) and $(Cp^*IrCl_2)_2$ (30 mg, 0.05 mol %) were added. The mixture was heated at 120 °C bath temperature for 18 h. At this time the mixture was diluted with dichloromethane (10 mL) and washed with water (5 mL) three times and concentrated. The residue was then dissolved in dichloromethane and extracted three times with 1 N HCl (5 mL each time), and the combined aqueous phases were basified with NaOH to pH 10 and extracted three times with dichloromethane (10 mL each time). The resulting organic phase was dried with $MgSO_4$ and concentrated to provide 230 mg of crude product (69% yield) that was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, 1H), 7.27 (m, 1H), 7.03 (m, 1H), 2.70 (m, 3H), 2.25 (m, 2H), 2.20 (s, 3H), 1.30−1.20 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1 (d, 1C), 137.4 (d, 1C), 129.2 (s, 1C), 127.9 (d, 1C), 119.2 (d, 1C), 116.6 (d, 1C), 56.2 (s, 2C), 49.3 (m, 1C, $^{13}CD_2N$), 47.8 (m, 1C), 40.7 (d, 1C), 21.7(s, 2C), 19.3 (d, 1C). LC-MS (ES+) 274.2 (M + H, M + 5 isomer).

3-Phenyl-*N*-(1-phenylethyl)propan-1-amine Hydrochloride (23). 3-Phenylpropanol (10 mL, 1 equiv; 73.5 mmol), phenethylamine (9.45 mL, 1 equiv). and *N*-methylpyrrolidine (7.7 mL, 1 equiv) were combined in a 75 mL heavy-walled glass pressure vessel with a magnetic stirbar and Teflon bushing closure equipped with a perfluororo O-ring[45] (ChemGlass cat. no. GC-1880-30). Pentamethylcyclopentadienyliridium(III) chloride dimer (30 mg, 0.0005 equiv) was added in one portion. The headspace of the mixture was purged, and the vessel was sealed and heated in a 130 °C oil bath for 40 h, at which time the reaction had proceeded to 87% conversion. The volatiles were removed by coevaporation with 2-propanol, and the resulting yellow oil dried under reduced pressure. This material was dissolved in 25 mL

2-propanol, and hydrogen chloride (5 N in 2-propanol, 22 mL, 1.5 equiv) was added in one portion. Heptane (100 mL) was then added slowly, at which time the mixture became cloudy and the product crystallized from solution. An additional 50 mL of heptane was added to facilitate stirring, and the resulting white slurry was granulated for 18 h. At this time the white solids were isolated by filtration and were washed with 20 mL of a 1:4 mixture of 2-propanol/heptane and dried to provide 13.2 g (47.8 mmol, 65% yield) of the title compound. Mp 142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (br. s., 1 H) 9.82 (br. s., 1 H) 7.61−7.54 (m, 2 H) 7.45−7.33 (m, 3 H) 7.21−7.08 (m, 3 H) 7.04 (m, 2 H) 4.15 (dqd, J = 9.7, 6.9, 2.9 Hz, 1 H) 2.70−2.58 (m, 2 H) 2.58−2.41 (m, 2 H) 2.27−2.13 (m, 2 H) 1.83 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 135.9, 129.3, 129.2, 128.4, 128.2, 127.8, 126.1, 59.0, 45.1, 32.6, 27.2, 20.4.

■ ASSOCIATED CONTENT

Supporting Information. Synthesis and experimental procedures for the preparation of **2**, a full list of resins examined for Ir scavenging for **1**, ReactIR monitoring data for the reductive amination synthesis of **12**, an NMR in-process analysis for the reaction between **6** and **11**, and ^{1}H and ^{13}C spectra of **11**, **12**, **22**, **23**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +1-860-715-2505. E-mail: martin.a.berliner@pfizer.com.

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(1) Leading reviews: (a) Surry, D.; Buchwald, S. *Angew. Chem., Int. Ed* **2008**, *47*, 6338–6361. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177–2250.

(2) For a review, see: Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611–1641.

(3) (a) Lebel, L.; Tunucci, D.; Valentine, J.; Lowe, J. A., III; Hou, X.; Schmidt, C.; David Tingley, F., III; McHardy, S.; Kalman, M.; DeNinno, S.; Sanner, M.; Ward, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2974–2976. (b) For a review, see: Wolkenberg, S.; Sur, C. *Curr. Top. Med. Chem.* **2010**, *10*, 170–186.

(4) Brighty, K.; Castaldi, M. *Synlett* **1996**, 1097–1099. We utilized a different route to prepare **2** to facilitate safe execution on scale. See the Supporting Information.

(5) A recent report (Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451–3479) analyzing the types of reactions utilized in current medicinal chemistry publications has found that ca. 65% of all transformations are bond-forming processes, and of those, over 80% are C−N bond-forming reactions, with C−C bond-forming reactions a distant second at 15%. In the direct experience of this author this trend toward late-stage fragment assembly through carbon−heteroatom coupling reactions has become much more prevalent over the past decade.

(6) A rapid development timeline dictated that we commit to raw materials ordering before route selection. Consequently, **2**, **6**, and **8** were selected to allow for maximum flexibility in choosing a manufacturing route for the initial batch of **1**.

(7) (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press Inc.: San Diego, CA, 1985. (b) For a representative procedure, see: Aurelio, L.; Box, J. S.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, M. M. *J. Org. Chem.* **2003**, *68*, 2652–2667.

(8) For an example of a reaction where debenzylation proceeds in the presence of formaldehyde, see: Kende, A. S.; Liu, K.; Brands, K. M. J. *J. Am. Chem. Soc.* **1995**, *117*, 10597–10598. It appears that increased catalyst loading is necessary to retain catalytic activity.

(9) If not removed, small amounts of unreacted formaldehyde (as polymer) retained in crude isolates of **11** resulted in formation of *N*-methyl derivatives of amine **6** and **12** in the next step (see Figure 2).

(10) (a) Mancuso, A.; Swern, D. *Synthesis* **1981**, 165–185. (b) Tidwell, T. *Synthesis* **1990**, 857–870.

(11) Kim, K. S.; Cho, I. H.; Yoo, B. K.; Song, Y. H.; Hahn, C. S. *J. Chem. Soc., Chem. Commun.* **1984**, 762–763.

(12) Parikh, J. R.; Doering, W. V. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(13) Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(14) Due to lack of a chromophore, the initial reaction completion and product quality assays were typically conducted using GC and NMR, with the best data obtained by taking NMR spectra of aliquots of the reaction mixture.

(15) Imine **14** is not stable to HPLC analysis or TLC, unlike the imine product by condensation of *N*-Boc-protected aldehyde **5** and amine **6**. See the Supporting Information for analytical and reaction monitoring details for this sequence.

(16) Granular $NaBH_4$ was employed to reduce contact reactivity with the methanol-rich solution of imine during addition.

(17) First, aqueous sodium hydroxide was added to quench unreacted borohydride and break the amine-boron complex, which otherwise persisted after an aqueous work-up and complicated product isolation. Removal of methanol and of triethylamine and pyridine via azeotropic distillation with water gave a biphasic mixture that was extracted with ethyl acetate and then exchanged to 2-propanol.

(18) Activated DMSO reagents are known to react with base at elevated temperatures to provide methylthiomethyl electrophiles via Pummerer rearrangement. See, for example: van der Linden, J. J. M.; Hilberink, P. W.; Kronenburg, C. M. P.; Kemperman, G. J. *Org. Process Res. Dev.* **2008**, *12*, 911–920. This process was demonstrated by running this reaction using DMSO-d_6 as solvent, which resulted in formation of d_2-methylated (M + 16) isomers of **16** and **17**.

(19) For an example preparation of a labeled benzonitrile, see: Matloubi, H.; Shafiee, A.; Saemian, N.; Shirvani, G.; Daha, F. J. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 31–36.

(20) Khurana, J. M.; Kukreja, G *Synth. Commun.* **2002**, *32*, 1265–1269.

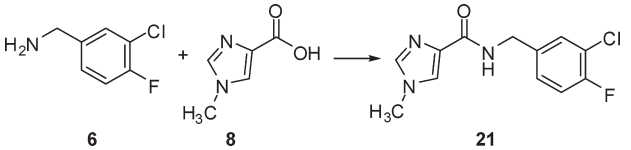
(21) Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687–2690.

(22) Krische and co-workers have postulated that deprotonation of an iridium(III) hydride by a carbonate base resulting in formation of an iridium(I) species is a key step in the enantioselective coupling between alcohols and allyl nucleophiles. See: Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, 7278 and references therein.

(23) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725.

(24) Personal communication from Pfizer colleague Dr. Robert A. Singer.

(25) Amide **21** is a byproduct formed in the final step from acylation of **6** with **8**. We could not separate **21** from **1** by nonchromatographic methods.



6 8 21

(26) Resins currently marketed for iridium removal postdate this work but were tested on **1** and did not provide useful reductions in iridium content. See the Supporting Information for full details.

(27) The fixed reactors in our kilolab are equipped with descending condensers. U-Shaped vapor traps are installed on the distillate return piping to prevent reflux vapors from reaching the condenser.

(28) For this compound, we observed cracking and channeling immediately after the last rinse solvent had been pushed through the filtercake. Cracking was prevented by halting the filtration and adding additional rinse solvent when the liquor level was approx 0.5−1 cm above the cake surface. Interestingly, not all batches of crystallized **12** bis(HCl) salt demonstrated this tendency.

(29) Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943–1954.

(30) Timing constraints necessitated that we focus on improvements to the existing Ir-catalyzed chemistry. Plans to reinvestigate the effectiveness of other Ir- and Ru-derived catalysts were abandoned as a result of the discontinuation of this project.

(31) After the completion of this optimization effort, we determined that inorganic carbonate bases or water proved to be unnecessary to achieve high turnover numbers (TONs). Stronger aqueous bases (NaOH, R_4NOH) led to catalyst inactivation.

(32) A preliminary experiment under recirculating flow conditions (150 °C loop temperature, 10 min residence time, 30 h reaction time) generated a similar product distribution.

(33) Williams and co-workers have described the use of $(Cp^*IrI_2)_2$ in amination reactions in water in the absence of exogenous base. (a) Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev* **2010**, *14*, 1046–1049. (b) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, *46*, 1541–1543.

(34) Poor solubility of the mono-HCl salt of **12** results in significantly reduced reaction rates and lower terminal conversions in solvents other than CH_2Cl_2, even when excess base was employed.

(35) Only partial conversion of **12** to **1** was observed under Schotten−Baumann conditions due to competitive and extremely rapid hydrolysis of the water-soluble **22** to **8**.

(36) Sodium carbonate was employed to minimize amide hydrolysis.

(37) This mixture contains **1**·HCl and ionic components resulting from reaction of **1** with **22** and subsequent degradation.

(38) (a) Stare, M.; Laniewski, K.; Westermark, A.; Sjögren, M.; Tian, W. *Org. Process Res. Dev.* **2009**, *13*, 857–862. (b) Levin, D. *Org. Process Res. Dev.* **1997**, *1*, 182.

(39) The full results of this screen are described in the Supporting Information.

(40) This process (amine cross-coupling catalyzed by Cp*Ir complexes) has been documented by Williams and co-workers. Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7375–7378.

(41) Amine alkylation is also observed using more hindered bases. For example, reactions using diisopropylethylamine as base (0.05 or 1 equiv) generate the desired product and a variety of cross-coupled products resulting from amine exchange, including mixed *N*-ethyl and *N*-isopropyl amines. Higher temperatures appear to accelerate the amine exchange process.

(42) Balcells and co-workers have conducted a theoretical mechanistic study of this reaction using carbonate as the base. See: Balcells, D.; Nova, A.; Clot, E.; Gnanamgari, D.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2008**, *27*, 2529–2535.

(43) Fujita and Yamaguchi have recently described the $(Cp^*IrCl_2)_2$-catalyzed amination of sulfonamides with alcohols, which also proceeds with a catalyst loading of 0.05 mol % Ir. The increased acidity of the sulfonamide is responsible for this catalytic activity and a strong base (KO*t*-Bu) has been identified to be necessary to facilitate turnover. See: Zhu, M.; Fujita, K.; Yamaguchi, R. *Org. Lett.* **2010**, *12*, 1336–1339.

(44) See the Supporting Information for the NMR in-process analysis of this reaction.

(45) Viton O-rings that are shipped with this equipment have poor chemical compatibility with *N*-methylpyrrolidine.