JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Development of a Large Scale Asymmetric Synthesis of the Glucocorticoid Agonist BI 653048 BS H_3PO_4

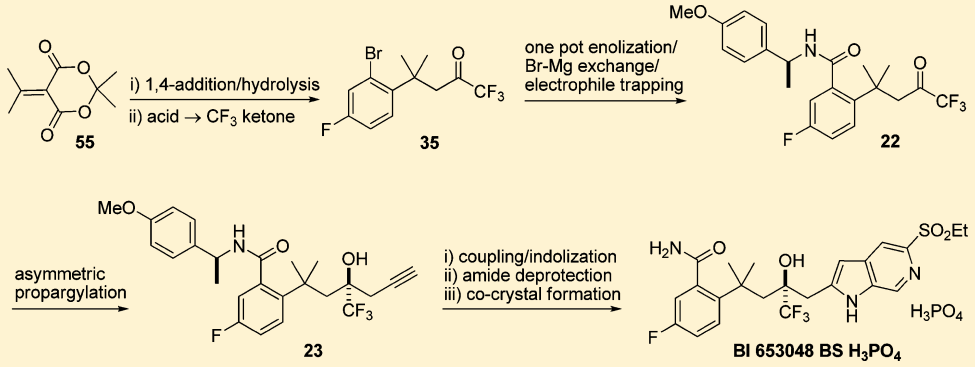
Jonathan T. Reeves,*[,†] Daniel R. Fandrick,[†] Zhulin Tan,[†] Jinhua J. Song,[†] Sonia Rodriguez,[†] Bo Qu,[†] Soojin Kim,[†] Oliver Niemeier,[§] Zhibin Li,[†] Denis Byrne,[†] Scot Campbell,[‡] Ashish Chitroda,[†] Phil DeCroos,[†] Thomas Fachinger,[§] Victor Fuchs,[†] Nina C. Gonnella,[‡] Nelu Grinberg,[†] Nizar Haddad,[†] Burkhard Jäger,[§] Heewon Lee,[†] Jon C. Lorenz,[†] Shengli Ma,[†] Bikshandarkoil A. Narayanan,[†] Larry J. Nummy,[†] Ajith Premasiri,[†] Frank Roschangar,[†] Max Sarvestani,[†] Sherry Shen,[†] Earl Spinelli,[†] Xiufeng Sun,[†] Richard J. Varsolona,[†] Nathan Yee,[†] Michael Brenner,[§] and Chris H. Senanayake[†]

[†]Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Old Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut, 06877-0368, United States

[‡]Analytical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Old Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut, 06877-0368, United States

[§]Boehringer Ingelheim GmbH & Co. KG, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

Supporting Information



ABSTRACT: The development of a large scale synthesis of the glucocorticoid agonist BI 653048 BS H_3PO_4 (**1**·H_3PO_4) is presented. A key trifluoromethyl ketone intermediate **22** containing an *N*-(4-methoxyphenyl)ethyl amide was prepared by an enolization/bromine−magnesium exchange/electrophile trapping reaction. A nonselective propargylation of trifluoromethyl ketone **22** gave the desired diastereomer in 32% yield and with dr = 98:2 from a 1:1 diastereomeric mixture after crystallization. Subsequently, an asymmetric propargylation was developed which provided the desired diastereomer in 4:1 diastereoselectivity and 75% yield with dr = 99:1 after crystallization. The azaindole moiety was efficiently installed by a one-pot cross coupling/indolization reaction. An efficient deprotection of the 4-methoxyphenethyl group was developed using H_3PO_4/anisole to produce the anisole solvate of the API in high yield and purity. The final form, a phosphoric acid cocrystal, was produced in high yield and purity and with consistent control of particle size.

INTRODUCTION

Traditional anti-inflammatory agents used for the treatment of rheumatoid arthritis are steroids such as prednisolone and dexamethasone.[1] While effective, these compounds unfortunately can cause undesirable side effects due to activation of the glucocorticoid receptor. It is therefore desirable to identify nonsteroidal glucocorticoids with increased selectivity that avoid the side effects of traditional steroidal agents. Compound **1**·H_3PO_4 (BI 653048 BS H_3PO_4) was identified by our Medicinal Chemistry Department as a candidate for development for the treatment of rheumatoid arthritis (Figure 1).[2] To support development work and clinical studies, a safe, scalable, and efficient synthesis of **1**·H_3PO_4 was required. Herein we present our results on the development of a large scale, asymmetric propargylation based synthesis of **1**·H_3PO_4.[3]

RESULTS AND DISCUSSION

The Medicinal Chemistry synthetic route to **1** is shown in Scheme 1.[2] The route relies on a diastereoselective addition of lithiated (*S*)-*p*-tolyl methyl sulfoxide **7** to trifluoromethyl ketone **6** to set the chiral center with 2:1 diastereoselectivity.[4] Other notable features of the synthesis are the elaboration of an

Received: January 21, 2013
Published: April 1, 2013

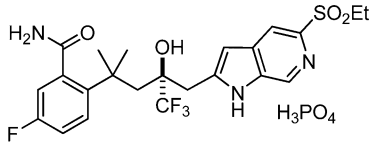
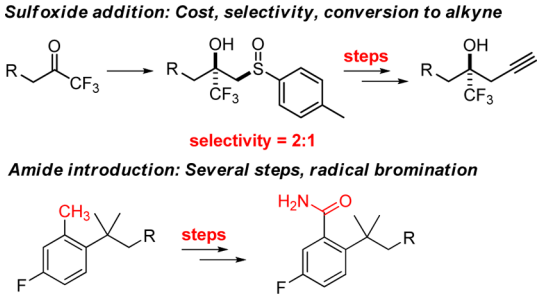


Figure 1. Structure of BI 653048 BS H_3PO_4.

aryl methyl group to the primary carboxamide, the conversion of the β-hydroxy sulfoxide into a homopropargylic alcohol, and the synthesis of the azaindole via Sonogashira cross coupling of alkyne **19** with iodide **20** followed by a base-mediated indolization of **21**.[5] The synthesis proceeds in 17 linear steps with an overall yield of 0.8%.

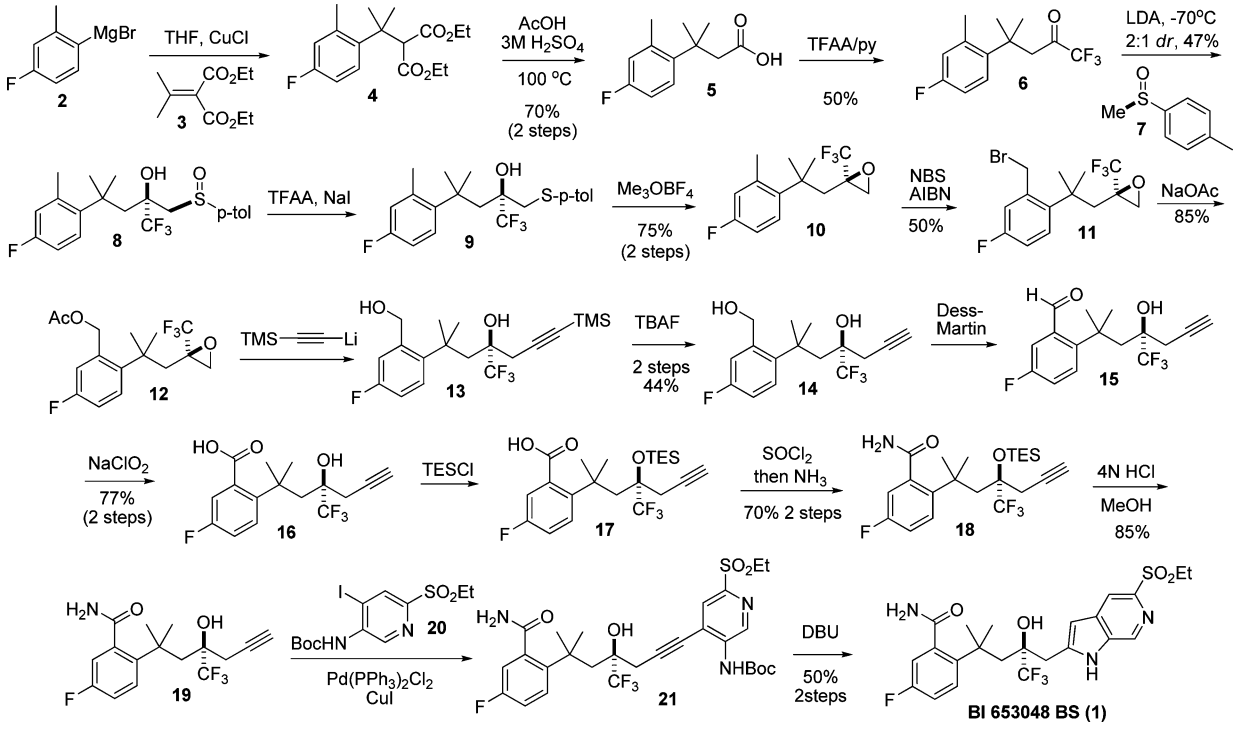
On evaluation of the discovery route for potential scale-up, several key concerns were identified (Scheme 2).[6] First, the introduction of the chiral center proceeded with moderate selectivity, employing the expensive chiral sulfoxide **7**,[7] and several steps were required to elaborate the β-hydroxy sulfoxide **8** into the homopropargylic alcohol moiety necessary for the Sonogashira cross coupling. Second, the conversion of the aryl methyl group into the primary carboxamide required several steps, including a radical bromination. The radical bromination posed a significant safety concern as a potential runaway reaction.[8] Finally, the length and low overall yield of the synthesis meant a large investment in raw materials and manpower would be required for direct scale-up of the current route. On the other hand, the late stage installation of the azaindole unit by a cross coupling/cyclization sequence was attractive, as was the general strategy for installing the chiral center by addition of a nucleophile to a trifluoromethyl ketone. With these points in mind, we set out to design a more efficient and scalable route to **1**.

Scheme 2. Key Challenges for Scale-up of the Medicinal Chemistry Synthesis



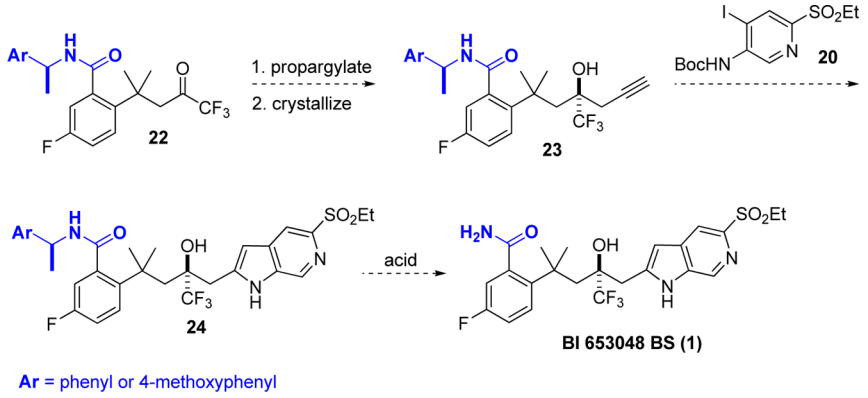
After extensive route-scouting, we arrived at the "chiral amide" route as the most promising and direct synthesis of **1**. This route addressed the two key issues identified in the Medicinal Chemistry route, while maintaining the cross-coupling/cyclization strategy for late-stage heterocycle introduction. The overall concept for this route is shown in Scheme 3. A propargylation of trifluoromethyl ketone **22** would directly install the requisite homopropargyl alcohol in **23** and would avoid the need for any functional group manipulations as with the chiral sulfoxide addition. A chiral *N*-phenethyl amide in the trifluoromethyl ketone substrate **22** would serve multiple purposes. First, it would potentially render the propargylation diastereoselective. Second, the diastereomeric hydroxy amides produced in the propargylation reaction might be separable by crystallization. Lastly, the phenethyl group could be removed under acidic conditions to give the required primary carboxamide directly, thereby avoiding the extensive functional group manipulations and oxidation state adjustments of the Medicinal Chemistry route.[9] Employing the same cross coupling/cyclization sequence for late-stage installation of the

Scheme 1. Medicinal Chemistry Synthesis of 1

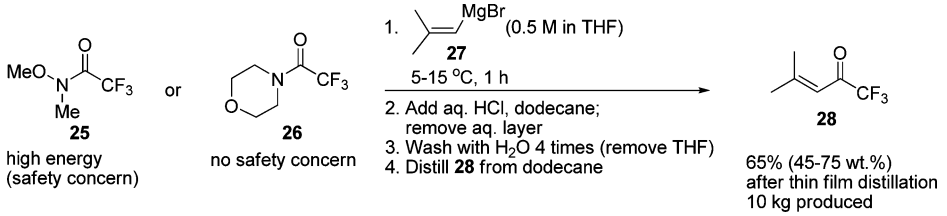


dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

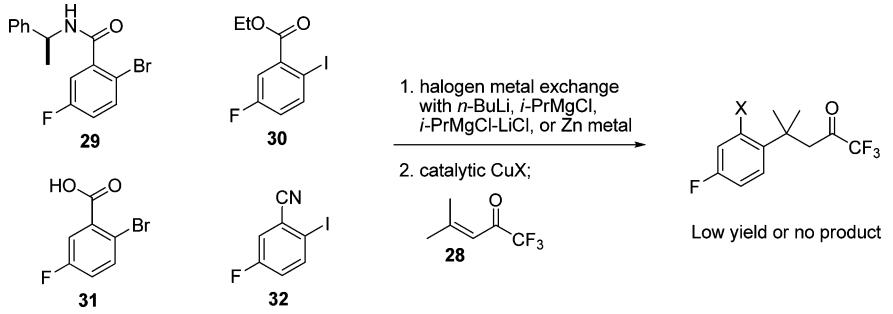
Scheme 3. Concept for Chiral Amide Route



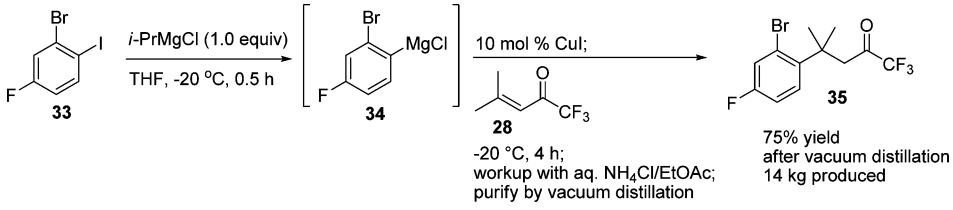
Scheme 4. Synthesis of Trifluoromethyl Enone 28



Scheme 5. Unsuccessful Conjugate Additions to Enone 28



Scheme 6. Conjugate Addition to Enone 28



azaindole would provide **24**, from which the phenethyl group could be removed with acid to give **1**.

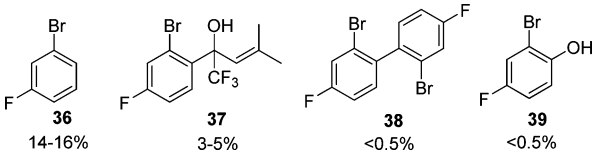
The first challenge in the demonstration of the chiral amide route was the development of a synthesis of the amide trifluoromethyl ketone **22**. The conjugate addition of aryl Grignard reagents to enone **28** was developed in our Medicinal Chemistry Department and appeared to be a potential route to ketone **22** (Scheme 4).[1,2,10] The enone **28** was prepared by addition of commercially available 2-methyl-1-propenylmagnesium bromide **27** to the *N*-trifluoroacetyl Weinreb amide **25**. After routine reaction safety analysis showed the reagent **25** to be a high energy compound, we switched to the analogous morpholine amide **26**, which eliminated any safety concerns and gave the same yield and quality as **25**.[11] Enone **28** was prepared by adding the morpholine amide **26** to a 5 °C solution of Grignard reagent **27**. The isolation of this enone was challenging due to its low boiling point and solubility in water. A special workup/isolation protocol had to be devised. After aging for 0.5 h, the reaction was quenched with aqueous HCl. Dodecane was added, and the aqueous layer removed. Additional washes with water effected the removal of most of the THF, while the product enone remained in the dodecane layer. The enone was then distilled (bp 108 °C at 1 atm) from the higher boiling dodecane (bp 217 °C at 1 atm) either by simple vacuum distillation on lab scale or by thin film distillation on kilogram scale. This process provided enone **28** as a 45−75 wt% solution in THF with small amounts of dodecane. This process was used to prepare 10 kg of **28**.

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

The conjugate addition of arylmetal reagents already functionalized with the amide or an equivalent oxidation state functional group to enone **28** was initially explored (Scheme 5). Unfortunately, the reagents derived from halogen-metal exchange of halides **29**−**32** in the presence of various copper salts led to either very low yields, exclusive 1,2-addition, or no reaction at all under a variety of reaction conditions.

We next explored the conjugate addition of the aryl Grignard derived from commercially available 2-bromo-4-fluoro-1-iodobenzene **33** (Scheme 6). If successful, the aryl bromide could potentially be elaborated into an amide by a subsequent aminocarbonylation reaction. The Knochel procedure for generation of the requisite aryl Grignard **34** from iodobenzene **33** was employed.[12] Iodine−magnesium exchange was found to occur within 30 min using isopropylmagnesium chloride in THF at −20 °C. Subsequent addition of 10 mol % CuI followed by enone **28** gave the crude ketone **35** after workup with aqueous NH_4Cl and EtOAc, which was further purified by vacuum distillation to give highly pure (>95 wt%) bromoketone **35**. The distillation was required to remove byproducts and impurities which are shown in Scheme 7. Proto-quenched

Scheme 7. Structures and Quantities of Impurities Generated in the Conjugate Addition Step



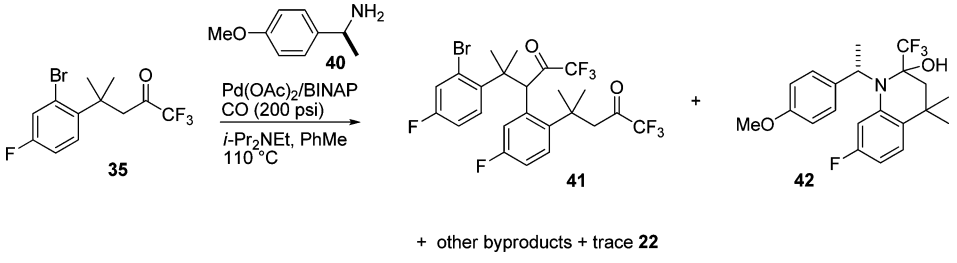
Grignard byproduct **36** and 1,2-addition byproduct **37** were the major impurities. The dimer **38** and phenol **39** were generated in small amounts, provided the reaction was maintained under a rigorously oxygen-free atmosphere. In one kilo-lab batch, an accidental introduction of air caused large amounts of dimer **38** (16%) and phenol **39** (3.4%) to be generated. The dimer formation can be explained by the known dimerization of aryl cuprates in the presence of oxygen,[13] while the phenol formation likely resulted from reaction of the aryl Grignard reagent with oxygen.[14] This conjugate addition reaction was used to prepare 14 kg of **35**.

With the bromoketone **35** in hand, we investigated methods to convert the aryl bromide into the *N*-4-methoxyphenethylamide.[15] Initial efforts focused on aminocarbonylation to install the amide.[16] The direct aminocarbonylation of **35** under all conditions investigated gave a complex mixture of products, from which only trace amounts of the desired product **22** were detected (Scheme 8). The starting material **35** was rapidly consumed under the reaction conditions. By LC-MS analysis of the reaction mixture, byproducts with masses corresponding to structures **41** and **42** were detected. Byproduct **41** arises from coupling of the enolate of **35** with the aryl bromide, and **42** could form from direct amination of **35** or, alternatively, by initial hemiaminal formation followed by intramolecular C−N bond formation.

Given the observed sensitivity of the free trifluoromethyl ketone substrate, protection of the ketone as a dioxolane prior to aminocarbonylation was subsequently explored. Under standard conditions for acetal formation (catalytic acid, ethylene glycol, azeotropic removal of water) no product was formed, even after extended reaction times. This observation was consistent with the literature on trifluoromethyl ketones, which have been shown to be highly resistant to acid catalyzed ketalization due to the electron withdrawing effect of the trifluoromethyl group, which disfavors adjacent oxonium ion formation.[17] By switching to basic reaction conditions using 2-chloroethanol, however, the desired dioxolane **43** was formed in excellent yield (Scheme 9).[18] The aminocarbonylation of **43** with amine **40** proceeded smoothly to give the amide **44**. Deprotection of the dioxolane group proved to be challenging, again due to the electronic effect of the trifluoromethyl group. Standard acid catalyzed hydrolysis was completely ineffective, as was the use of strong Lewis acids such as $TiCl_4$. It is known that trifluoromethyl ketone ketals may be deprotected under dealkylative conditions with boron trihalides.[16] These conditions were successful in partially deprotecting the ketal, but concomitant demethylation of the aryl methoxy group to give **45** as well as other side reactions could not be avoided.

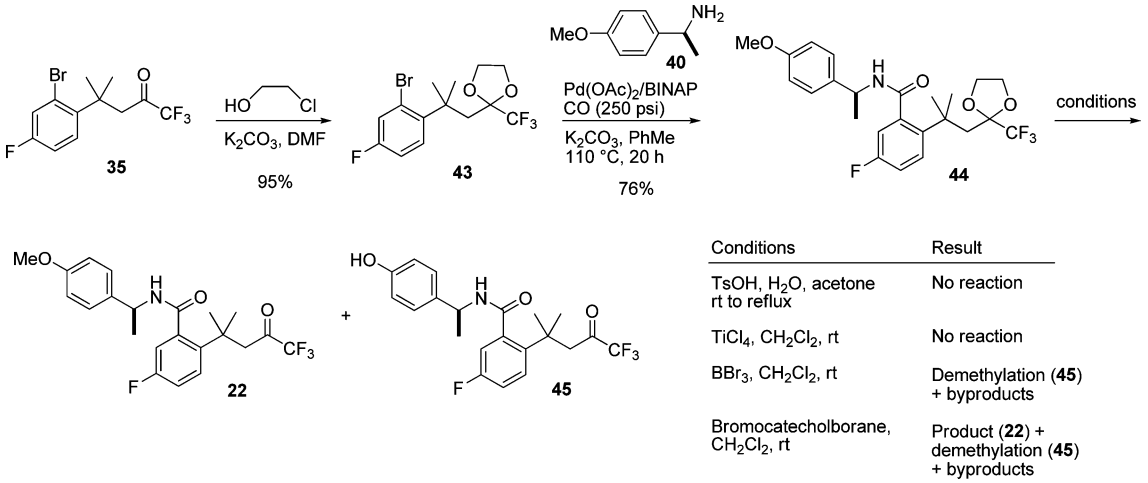
Due to the difficulties encountered in developing an aminocarbonylation route to **22**, a more direct alternative route was explored. A process in which the amide would be introduced by conversion of the aryl bromide to a Grignard reagent and subsequent trapping with isocyanate **46** was envisioned (Scheme 10).[19] To avoid deprotection of the dioxolane group, an *in situ* "protection" of the trifluoromethyl ketone as its enolate was proposed. The enolate should be stable to reagents used for bromine/metal exchange, and the ketone would be regenerated during aqueous quench of the reaction mixture. Due to the low pK_a of trifluoromethyl ketones, enolization should be facile, and furthermore, the nucleophilicity of the enolate should be low, thus minimizing competitive attack of the enolate on the isocyanate. The base to be used for enolization needed to fulfill several requirements. First, it must not generate a species after ketone deprotonation which could be deprotonated on the subsequent addition of organomagnesium reagents for bromine−magnesium exchange. This excluded typical alkoxide or amide bases which would generate alcohols or amines after deprotonation. Second, it could not generate a species after ketone deprotonation which could react with the isocyanate. This requirement also excluded alkoxide or amide bases. Finally, it could not be a nucleophilic

Scheme 8. Attempted Aminocarbonylation of 35

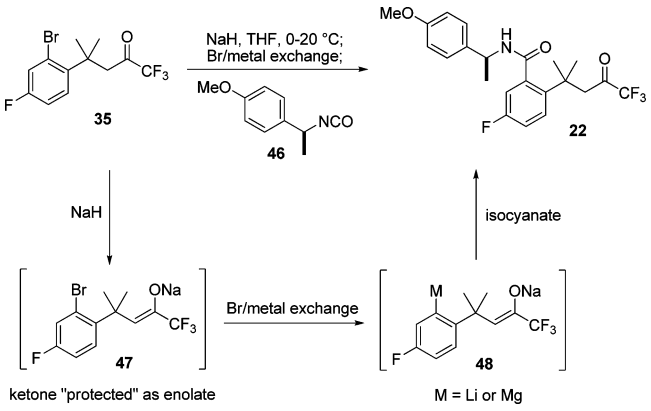


dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

Scheme 9. Aminocarbonylation of a Protected Substrate



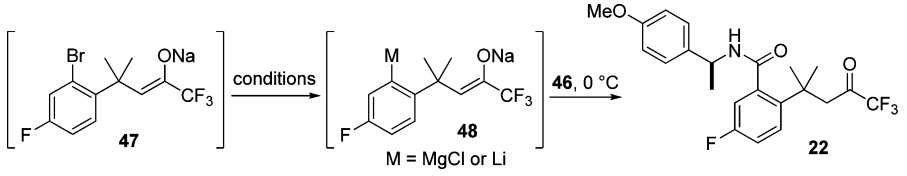
Scheme 10. Concept for One-step Conversion of 35 to 22 via Enolization/Bromine Exchange/Isocyanate Quench



base, since this would result in competitive addition to the trifluoromethyl ketone instead of enolization. This requirement excluded most organolithium and organomagnesium bases. With these restrictions in mind, sodium hydride seemed a logical choice since it generates only hydrogen gas as a byproduct and it is not nucleophilic. Treatment of **35** with an excess (1.2 equiv) of NaH (60 wt% in mineral oil) in THF at rt resulted in smooth generation of H_2 gas and the formation of sodium enolate **47**, as confirmed by React-IR measurements (*vide infra*). Aging experiments showed enolate **47** to undergo no decomposition on aging at rt for several days.

Bromine−metal exchange of enolate **47** was investigated with several reagents (Table 1). The use of *n*-BuLi at −65 °C resulted in fast and complete exchange. Subsequent trapping with isocyanate **46** provided ketone **22** in low yield (25%), accompanied by many byproducts (entry 1). Despite the low yield, this result was encouraging in that it validated the ketone "protection" as an enolate strategy. The use of 0.4 equiv of lithium tributyl magnesiate at 0 °C resulted in a fast exchange, with the bromide being consumed within 15 min (entry 2). Quenching with isocyanate **46** and workup resulted in a 53% isolated yield of **22** after chromatography. The use of either isopropylmagnesium chloride (entry 3) or isopropylmagnesium chloride lithium chloride complex (Turbo Grignard, entry 4) resulted in low conversions after 24 h at rt.[20] Knochel and co-workers have described the use of Turbo Grignard in combination with ∼2 equiv of 1,4-dioxane to generate the highly active exchange reagent "*i*-Pr_2Mg-LiCl".[21] The 1,4-dioxane serves to drive the Schlenk equilibrium toward the dialkylmagnesium reagent by precipitation of $MgCl_2$-dioxane complex. By adding 2 equiv of 1,4-dioxane to the reaction with

Table 1. Screening of Reagents for Bromine−Metal Exchange



entry	conditions	conversion (%)[a]	yield (%)
1	*n*-BuLi (1 equiv), −65 °C, 15 min	100	25[b]
2	*n*-Bu_3MgLi (0.4 equiv), 0 °C, 15 min	100	53[b]
3	*i*-PrMgCl (1.2 equiv), rt, 24 h	<5	
4	*i*-PrMgCl-LiCl (1.2 equiv), rt, 24 h	10	
5	*i*-PrMgCl (1.2 equiv), dioxane (2 equiv), rt, 24 h	40−85	
6	*i*-PrMgCl-LiCl (1.1 equiv), dioxane (2 equiv), rt, 5 h	>98	85[c]

[a]Conversion of bromine−metal exchange of **47** to **48** as measured by HPLC analysis of reaction aliquots quenched into H_2O. [b]Isolated yield of **22** after quenching with isocyanate **46**, workup, and purification by chromatography on SiO_2. [c]Isolated yield of **22** after quenching with isocyanate **46**, workup, and purification by crystallization.

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

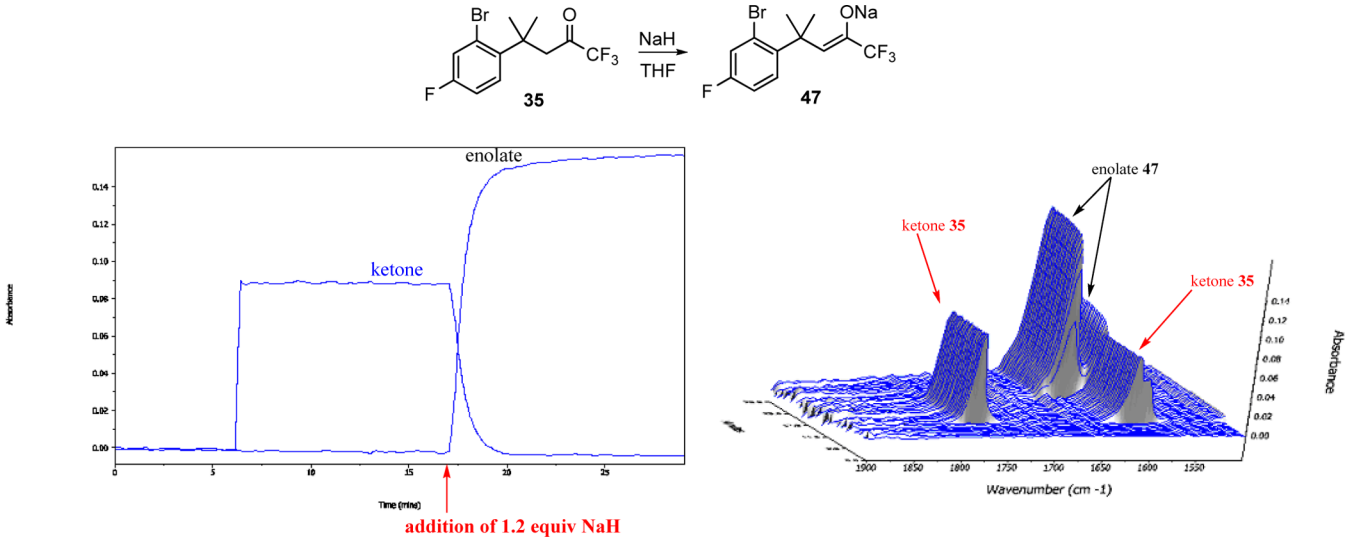


Figure 2. Monitoring of the enolization of **35** with React IR.

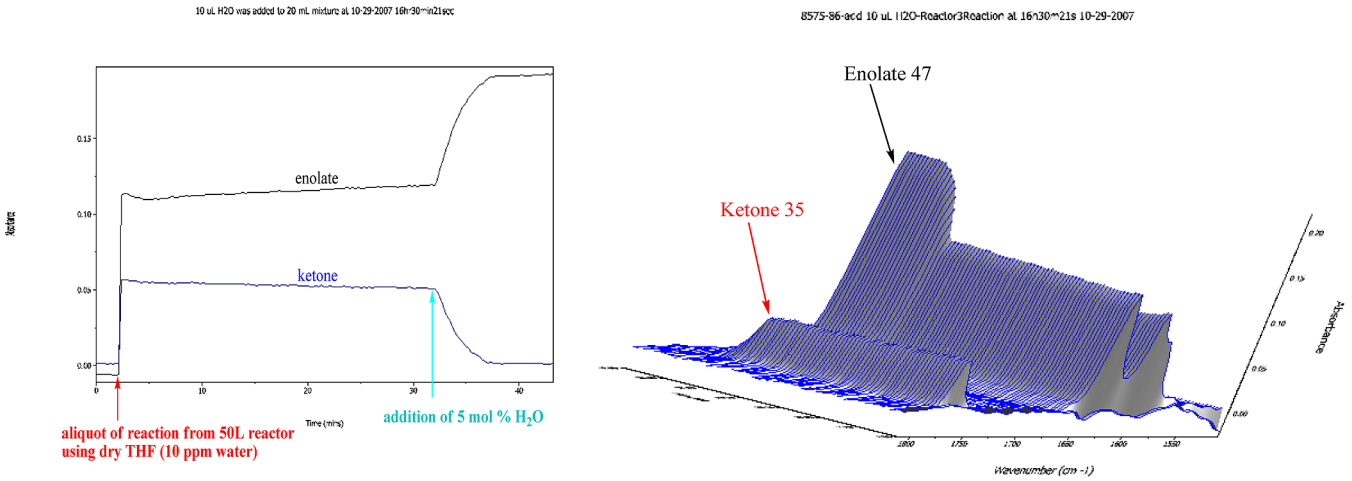
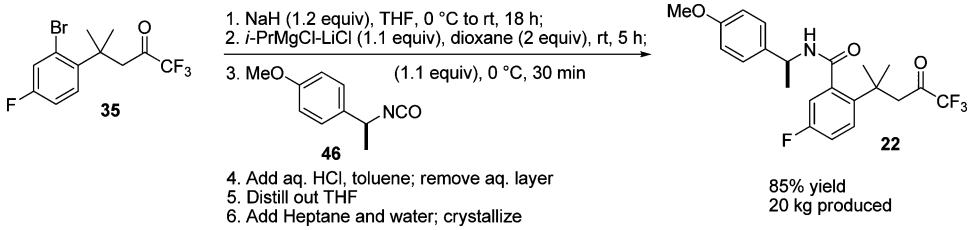


Figure 3. Acceleration of the enolization of **35** on addition of water.

Scheme 11. Optimized Procedure for the Synthesis of Chiral Amide Ketone 22



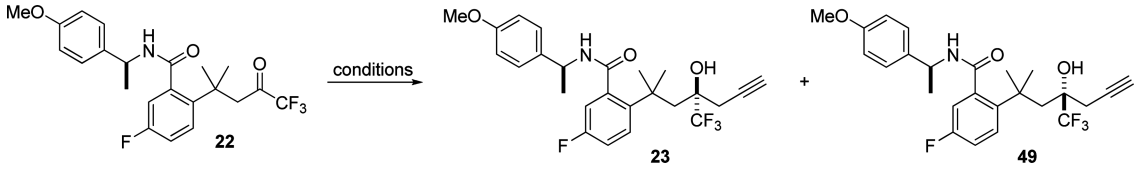
Turbo Grignard (entry 6), a dramatic acceleration in the exchange was observed, and complete consumption of the bromide was achieved after 5 h at rt. In this case, a clean reaction profile was achieved, and the product **22** was isolated in 85% yield after crystallization. Adding dioxane to the reaction with isopropylmagnesium chloride (entry 5) was also effective in accelerating the exchange, although in this case the rate was inconsistent from batch to batch, and did not reach complete conversion as with Turbo Grignard/dioxane.

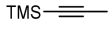
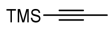
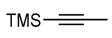
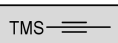
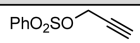
The enolization of **35** was effectively monitored by React IR. The carbonyl absorbance of **35** at ~1750 cm^{-1} disappears on addition of 1.2 equiv of NaH to a THF solution of **35** at 0 °C and new absorptions attributable to the enolate **47** appear (Figure 2).

This technique was particularly beneficial on scale-up of the reaction, when a critical dependence of the enolization rate on the water content of the reaction mixture was observed. Laboratory batches typically used THF containing 100−500 ppm water. On scaling to a 4 kg reaction in a 50 L reactor, however, the THF used from a 200 L drum was extremely dry (~10 ppm water). The enolization was found to be much slower for this reaction. After 18 h at rt, only ~50% enolization had occurred, compared with laboratory scale batches in which the enolization was always completed after 0.5−1 h. On addition of a catalytic amount (5 mol %) of water to aliquots of

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

Table 2. Screen of Propargylation Conditions



entry	propargyl source	reaction conditions	conversion (%)[a]	dr[b] 23:49	yield (%)[c,d] of 23 + 49	yield (%)[e] of 23 (dr)[f]
1		Al, $HgCl_2$ (5 mol %), THF, rt	100	1:1	90	30 (99:1)
2		Zn, THF, 70 °C	100	1:1	87	31 (99:1)
3		*n*-BuLi, TMEDA, THF, -70 °C, 30 min; then **22**	30	1:1	-	-
4		*n*-BuLi, TMEDA, THF, -20 °C, 30 min; then $MgBr_2$ (1.1 equiv), -20 °C, 30 min; then **22**	30	1:1	-	-
5		*n*-BuLi, TMEDA, THF, -20 °C, 30 min; then $ZnBr_2$ (1.1 equiv), -20 °C, 30 min; then **22**	Variable (0-85)	1:1	-	-
6		*n*-BuLi, THF, -20 °C, 30 min; then $ZnBr_2$ (1.1 equiv), -20 °C, 30 min; then **22**	98	1:1	94	33 (98:2)
7		Et_2Zn, $PdCl_2$dppf (5 mol %) THF, rt	46	1:1	-	-

[a]Conversion of **22** to **23** + **49** as measured by HPLC analysis of reaction aliquots quenched into H_2O. [b]Diastereomeric ratio of **23** to **49** measured in the reaction mixture by HPLC analysis prior to workup. [c]HPLC assay yield. [d]For entries 3−6, the crude product was first treated with NaOMe/MeOH to remove the alkynyl TMS group. [e]Isolated yield of **23** after crystallization from hexanes/EtOAc. [f]Diastereomeric ratio of **23** to **49** measured in the crystallized, isolated **23** by HPLC analysis.

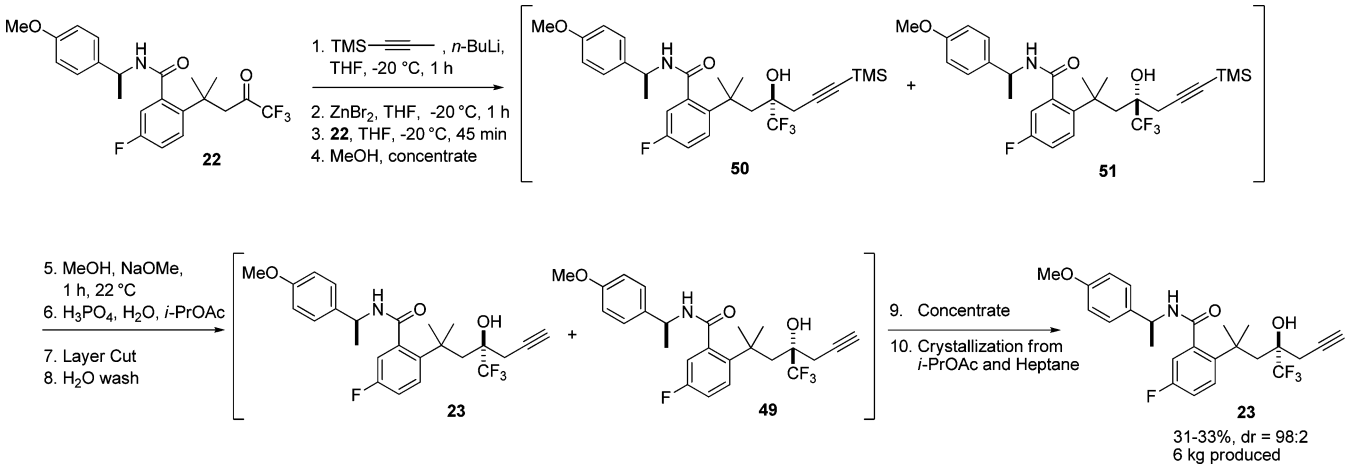
the reaction mixture, however, the enolization rapidly went to completion (Figure 3). The acceleration of the enolization could also be effected by the addition of catalytic amounts of alcohols, though with lesser efficiency.[22] In order to ensure reproducibility on scale-up, a specification for water content of the THF was set at 300−500 ppm water. With this specification as well as in process monitoring by React IR, the enolization gave reproducible results.

The optimized conditions for conversion of bromoketone **35** to chiral amide ketone **22** are shown in Scheme 11. After enolization and bromine/magnesium exchange, the reaction mixture was cooled to 0 °C and quenched with isocyanate **46**. After 30 min, the reaction mixture was quenched with aqueous HCl and toluene, and the aqueous layer separated. THF was distilled and the product crystallized out on addition of heptane and water. This process was employed to make the first 20 kg of **22**.

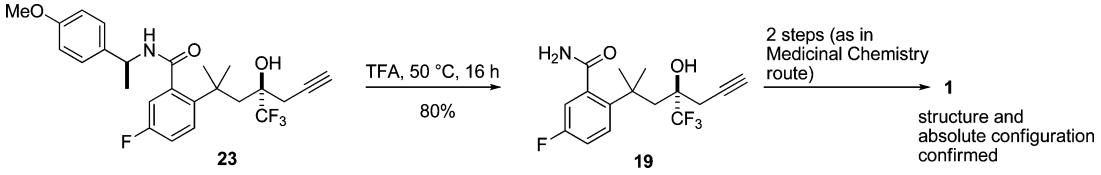
With the chiral amide ketone in hand, investigations into the propargylation reaction commenced. The reaction with propargyl bromide and Al metal in the presence of catalytic $HgCl_2$ gave a clean and complete conversion to a 1:1 mixture of the diastereomeric alcohols **23** and **49** (Table 2, entry 1). While the lack of diastereoselectivity was disappointing, we were gratified to find that recrystallization of the 1:1 mixture of **23** and **49** from hexanes/EtOAc gave a 30% yield of diastereomer **23** with a diastereomeric purity of 99:1. This eutectic controlled crystallization thus enabled us to obtain the challenging tertiary alcohol stereocenter in pure form, despite the nonselective propargylation reaction. We then screened further reagents and conditions for propargylation in the hopes of increasing the diastereoselectivity. The use of Zn metal gave access to the product in similar yield and selectivity (entry 2). While this was positive in that it removed toxic $HgCl_2$ from the process, we still faced a safety concern from the use of shock-sensitive propargyl bromide. Corey reported the deprotonation of 1-trimethylsilylpropyne with *n*-BuLi/TMEDA in Et_2O and the subsequent addition of the propargyl lithium species to alkyl halides and carbonyl compounds.[23] The application of the Corey conditions, only replacing Et_2O with THF, gave a low conversion to product with a dr of 1:1 (entry 3). Extensive variation of solvent and temperature led to no increase in the conversion. We speculated that the strongly basic propargyl lithium competitively enolized the trifluoromethyl ketone either directly or by initial deprotonation of the amide followed by intramolecular proton transfer and thereby shut down the carbonyl addition process. We then investigated transmetalation of the propargyl lithium reagent to magnesium (entry 4) and zinc (entries 5 and 6) in the hopes of generating a less basic species and avoiding deprotonation. While the use of $MgBr_2$ gave a low conversion as with the lithium reagent, the use of $ZnBr_2$ gave encouraging results, although they were not reproducible.[24] After extensive study of the reaction conditions, we found that TMEDA was the culprit for irreproducibility. Upon omission of TMEDA from the reaction, not only was the deprotonation of TMS propyne still effective, but the propargylation gave a consistently high conversion and clean reaction profile. The reasons for TMEDA shutting down the reaction are unclear. We speculate that the propargyl zinc

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

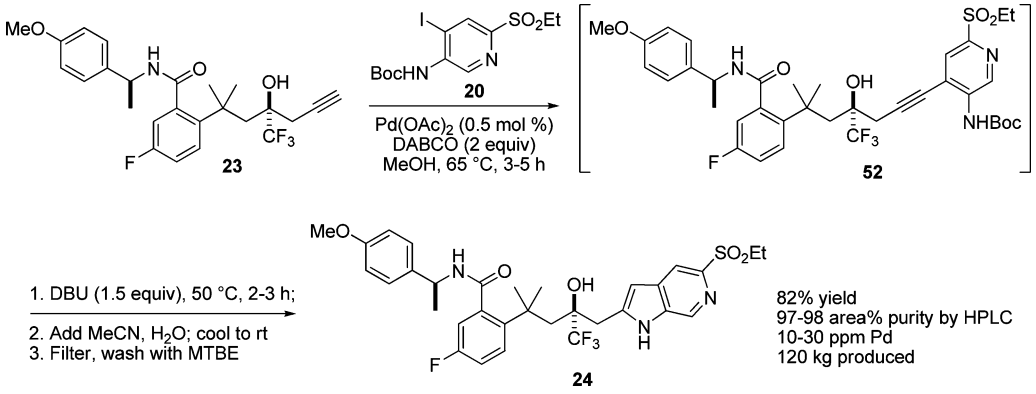
Scheme 12. Optimized Conditions for Nonselective Propargylation



Scheme 13. Deprotection of 23 and Proof of Structure and Stereochemistry



Scheme 14. One-Pot Cross Coupling/Cyclization of 23 to 24



species generated in the presence of TMEDA is likely coordinated by TMEDA, rendering it more electron rich and more basic, and thus more capable of causing enolization. Marshall's palladium catalyzed propargylation with propargyl benzenesulfonate (entry 7) was also investigated, but gave a low conversion with no diastereoselectivity.[25]

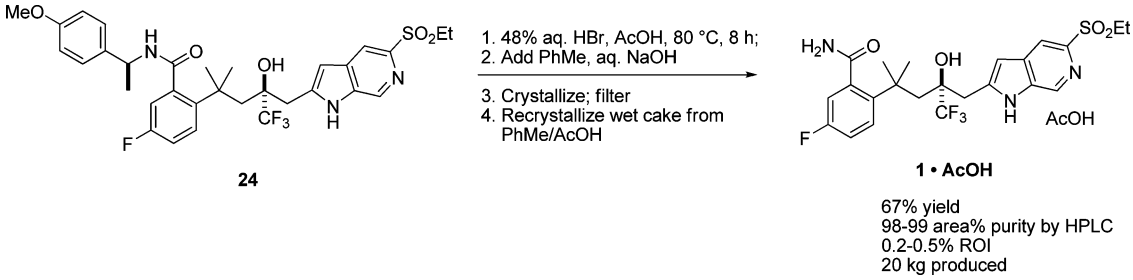
After the propargylation, a 1:1 mixture of the diastereomeric TMS alkynes **50** and **51** was produced (Scheme 12). Removal of the trimethylsilyl group could be accomplished in the same pot by quenching the propargylation reaction with MeOH and adding sodium methoxide (25 wt% in MeOH). After 1 h at rt, the proto-desilylation was complete, giving the diastereomeric alkynes **23** and **49**. Upon acidification and workup, a solution of the crude product in *i*-PrOAc was obtained, and after concentration and addition of heptane, the desired diastereomer **23** crystallized out in 31−33% yield with a dr of >98:2. This propargylation reaction in combination with the powerful crystallization enabled access to the key chiral intermediate in pure form, and 6 kg of **23** was produced using this procedure.

We next investigated the deprotection of the 4-methoxyphenethyl group. Literature procedures for removal of this group from amides included the use of TFA, TsOH, or H_2SO_4.[9] We found that heating a solution of **23** in neat TFA at 50 °C for 16 h gave the amide **19** in 80% yield (Scheme 13). Because amide **19** was also an intermediate in the Medicinal Chemistry route to **1** (see Scheme 1), we could confirm the structure of this intermediate by comparison. Furthermore, conversion of **19** by the same cross coupling/cyclization sequence into **1** confirmed the absolute configuration and structure. With these results, we had validated the chiral amide propargylation route.

There are two possible sequences of the last two conversions: the sequence employed above, with deprotection of the amide prior to heterocycle installation, or alternatively the heterocycle installation followed by amide deprotection. We preferred the latter sequence for two reasons. First, by moving the amide deprotection to the last chemical step, we allowed an additional step for removal of any residual Pd. If the cross coupling/cyclization was left as the last chemical step, residual Pd control might be more challenging. Second, by leaving the chiral amide

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

Scheme 15. Deprotection of 24 to 1·AcOH using HBr/AcOH



in place for an additional step, we would have another opportunity to enrich chiral purity in the crystallization after heterocycle installation. With this plan in mind, we investigated the cross coupling/cyclization reaction of **23**. The Medicinal Chemistry route employed a Sonogashira cross coupling of **19** with iodopyridine **20** to give the alkynyl pyridine **21**. This compound was then treated with DBU in MeOH to effect cyclization with concomitant loss of the Boc group to give the azaindole **1**. We suspected that these two reactions could be combined into a one-pot protocol. This proved possible by running the Sonogashira reaction with MeOH as the solvent, and adding DBU on completion of the cross coupling reaction. It was also found that excluding CuI from the reaction resulted in not only clean and complete conversion, but also eliminated the formation of an impurity derived from alkyne homocoupling. A screen of numerous Pd catalysts and bases for the cross coupling reaction was done. While numerous Pd catalysts were effective, $Pd(OAc)_2$ was found to be the optimal catalyst in terms of efficacy and cost. Of the bases screened (NaOMe, *N*-methylpyrrolidine, Et_3N, DBU, DABCO, quinuclidine, *i*-Pr_2NEt, piperidine, tetramethylguanidine) DABCO gave the best results. The use of DBU in the cross coupling reaction resulted in no reaction. Interestingly, having MeOH as solvent was critical to the success of the reaction. When other alcohols (EtOH, *n*-PrOH, *i*-PrOH) were used, large amounts of impurities were generated. The optimized procedure involved heating a mixture of alkyne **23**, iodide **20** (1.01 equiv), DABCO (2.0 equiv), $Pd(OAc)_2$ (0.5 mol %) and MeOH (2 volumes) at 65 °C for 3−5 h to effect the cross coupling to give intermediate **52** (Scheme 14). Addition of DBU (1.5 equiv) followed by heating 2 h at 50 °C provided the azaindole **24**. The product was crystallized after addition of acetonitrile and water and cooling to rt, and was isolated in 83% yield, with 97−98 area% purity by HPLC, and 10−30 ppm of residual Pd. Significant optimization of the crystallization conditions was done in order to minimize the amount of residual Pd in the product, and also to achieve a fast filtration of the solid. Initially, MTBE/water was charged after the reaction for crystallization. While this gave low levels of residual Pd in the product (30−70 ppm), the filtration rate of the solid in the pilot plant was slow. By switching to MeCN/water for the crystallization, a faster filtration rate was achieved, with even lower levels of residual Pd (10−30 ppm).

The deprotection of the 4-methoxyphenethyl group to produce **1** was then investigated. The use of neat TFA at 50−60 °C, as was done for the deprotection of the alkynyl substrate **23**, was also effective on **24**, and after 16−20 h a clean and complete conversion to **1** was achieved. The use of neat TFA was not desirable for scale-up, however, and therefore a further screen of acids was undertaken. The use of concentrated HCl, 50% aqueous H_2SO_4 or methanesulfonic acid at elevated temperatures (70−80 °C) was effective in removing the 4-methoxyphenethyl group, though with formation of several impurities. Published conditions using *p*-toluenesulfonic acid in toluene at 110 °C resulted in fast deprotection (<1 h) but with formation of large amounts of impurities.[9b] It was found that using HBr (48% aqueous) and AcOH (2 volumes and 4 volumes, respectively) at 80 °C for 8 h gave a relatively clean conversion to **1**. The reaction mixture was then treated with toluene and enough aqueous NaOH to neutralize all HBr. The toluene served to solubilize poly(4-methoxy)styrene generated in the reaction as the byproduct of the 4-methoxyphenethyl group. The product crystallized out as an AcOH solvate in 80−85% yield with a purity of ∼96% (Scheme 15). The wet cake could be recrystallized from toluene/AcOH to upgrade the purity to 98−99%, and the product was obtained in an overall yield of 67%. The product gave residue on ignition values of 0.2 up to 0.5%, indicating the presence of inorganic salts. This process was used for production of 20 kg of **1·AcOH**.

The final form of the drug was a phosphoric acid cocrystal. The cocrystal form exhibited desirable physicochemical properties, stability characteristics, and improved solubility and bioavailability compared to the free form. The free base **1**, with a pK_a value of 1.75, was unlikely to form a salt with phosphoric acid (pK_a = 2.15), but it formed a stable and consistent crystal form as a complex with phosphoric acid. The single crystal X-ray structure analysis resolved the structure as a cocrystal with 1:1 stoichiometry between phosphoric acid and the API, with hydrogen bonding interactions between phosphoric acid and the amide group of the free base (Figure 4).[26] The process for formation of **1·H_3PO_4** needed to not only provide the API in high purity but also control the particle size

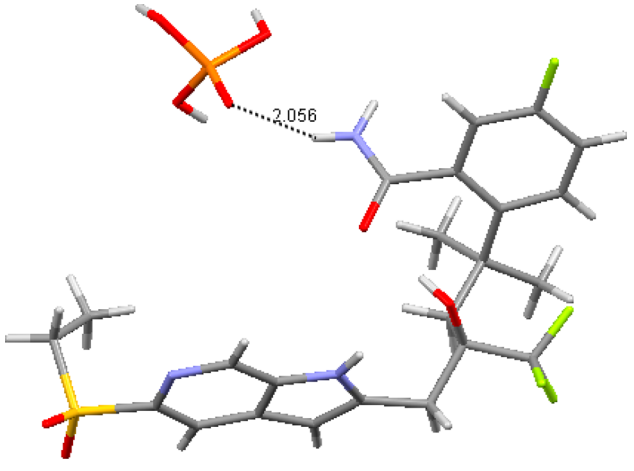
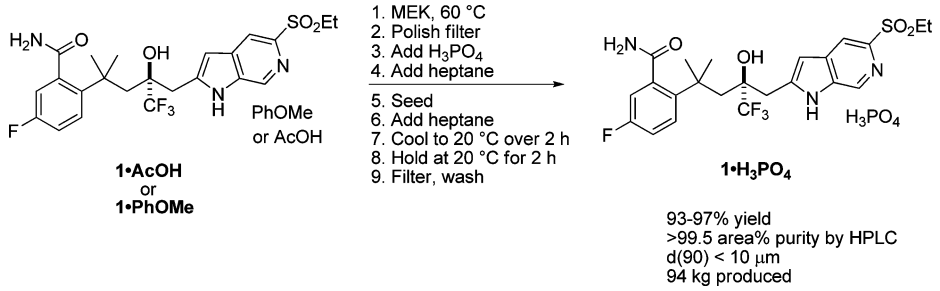


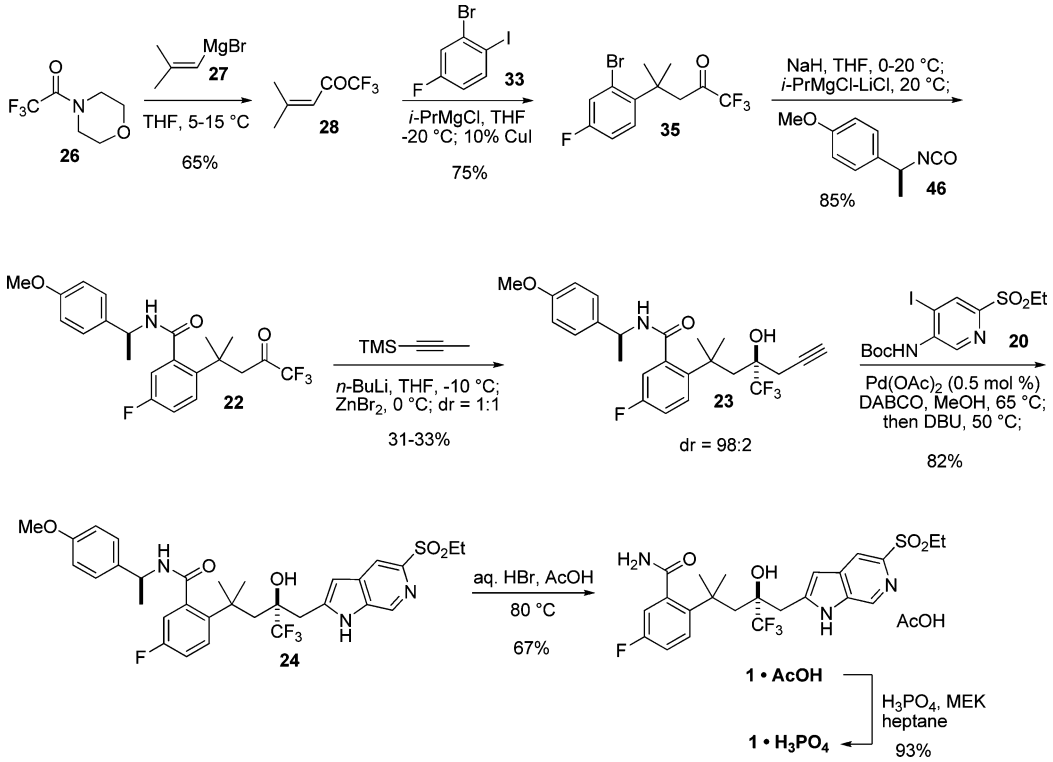
Figure 4. X-ray crystal structure of **1·H_3PO_4**. Hydrogen bonding interaction shown as dotted line.

dx.doi.org/10.1021/jo400079z | *J. Org. Chem.* 2013, 78, 3616−3635

Scheme 16. Phosphoric Acid Co-crystal Formation



Scheme 17. Nonselective Propargylation Route



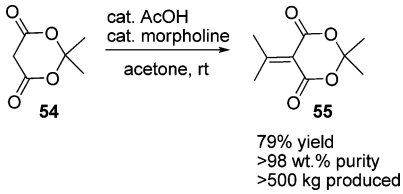
at a d(90) of <15 μm. The latter requirement arose from the inability to mill **1·H_3PO_4** without introducing amorphous content. A simple and robust process was developed as shown in Scheme 16. The AcOH solvate **1·AcOH** (or the anisole solvate **1·PhOMe**, *vide infra*) was dissolved in methyl ethyl ketone (MEK) at 60 °C, and the resultant solution was clean-filtered to remove any particulates. A slight excess (1.05 equiv) of 85% aqueous H_3PO_4 was charged at 50 °C, followed by heptane. The mixture was seeded, and additional heptane was added. The batch was cooled, filtered and the solid washed with MEK/heptane and finally heptane. The API was obtained in 93% yield from the AcOH solvate **1·AcOH** (or 97% yield from the anisole solvate **1·PhOMe**, *vide infra*) and in >99.5% purity by HPLC and with a consistent particle size of <10 μm. This process was employed to produce 94 kg of **1·H_3PO_4**.

The first generation route is summarized in Scheme 17. The route enabled the synthesis of **1** in 6 chemical steps plus 1 step for the final cocrystal formation, compared with the discovery route of 17 chemical steps. The overall yield was increased from 0.8 to 6.8%. To facilitate further scale-up some aspects of the synthesis required improvement. First, the need for a tedious distillation for purification of enone **28** was not desirable for large scale production. Second, isocyanate **46** required phosgene for its preparation, which posed a safety concern. In addition, the stability of isocyanate **46** was a concern, as a difficult to remove symmetrical urea impurity formed over time on exposure to air and moisture. These issues prompted investigations into a synthesis of chiral amide ketone **22** which did not proceed through enone **28** or isocyanate **46**. Next, the lack of diastereoselectivity in the propargylation reaction and the resultant low isolated yield of the product **23** greatly decreased the overall yield and throughput of the synthesis. The development of a diastereoselective propargylation was therefore critical. Finally, the modest yield obtained in the amide deprotection step, the need for recrystallization to upgrade the purity, the elevated salt content of the product, and the formation of poly(4-methoxy)styrene warranted an improved amide deprotection process which addressed these issues.

As a replacement of the enone **28**, we examined the chemistry of isopropylidene Meldrum's acid **55** (Scheme 18). This compound was prepared by Vogt and co-workers by the condensation of Meldrum's acid **54** with acetone in the presence of 4 Å MS, catalytic NH_4OAc, and toluene as solvent at rt.[27] Although this procedure was effective, the use of

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

Scheme 18. Preparation of Isopropylidene Meldrum's Acid 55

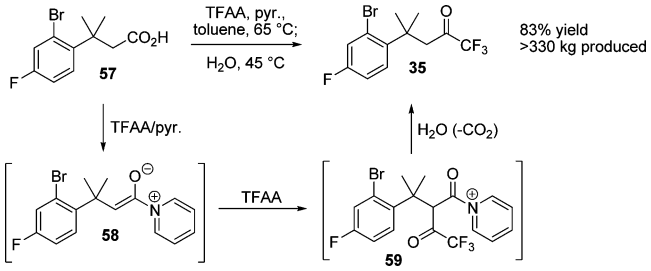


powdered 4 Å MS was not desirable for large scale operations. It was found that by using acetone as the reaction solvent, and catalytic amounts of AcOH and morpholine, **55** could be obtained in 79% yield. In this case the conversion of **54** to **55** did not reach completion, but rather ~90% conversion. The unreacted residual Meldrum's acid could conveniently be removed by a wash with aqueous NaOH. Importantly, **55** was a highly crystalline compound, and easily isolated in high purity by crystallization from MTBE/cyclohexane.

The conjugate addition of aryl Grignard reagent **34**, derived as previously described by iodine−magnesium exchange of aryl iodide **33** with *i*-PrMgCl, proceeded smoothly in the presence of 5 mol % CuI to give the adduct **56** in 84% yield (Scheme 19). Subsequently, it was found that the conjugate addition proceeded in the absence of CuI, and an even cleaner reaction profile was obtained in this case.[28] Heating **56** in a mixture of DMF and aqueous HCl promoted decarboxylative decomposition of the Meldrum's acid moiety and gave the crystalline acid **57** in 95% yield. These two steps were conveniently telescoped into a one-pot process. Thus, upon completion of the conjugate addition, the reaction was quenched with aqueous HCl, DMF was added, and the mixture was heated to 100 °C with concomitant distillation of THF and other volatiles. On completion of the hydrolysis/decarboxylation, the cooled reaction mixture was treated with aqueous HCl to effect the crystallization of **57** in 80% yield from **55**.[29]

The conversion of acid **57** into trifluoromethyl ketone **35** was accomplished as shown in Scheme 20. We have previously described the direct conversion of enolizable carboxylic acids to trifluoromethyl ketones by heating with TFAA and pyridine in toluene, followed by hydrolysis/decarboxylation on addition of water.[30] This procedure is a variation of that developed by Zard and co-workers for the conversion of acid chlorides to trifluoromethyl ketones.[31] Thus, treatment of acid **57** with TFAA (3 equiv) and pyridine (4.5 equiv) in toluene at 65 °C for 5 h followed by addition of water and heating an additional 1 h provided trifluoromethyl ketone **35** in 83% yield after extractive workup. Importantly, **35** generated from this reaction was free of the impurities generated by the previous CuI catalyzed conjugate addition to enone **28**, and consequently did not require purification by vacuum distillation. A concentrated

Scheme 20. Conversion of Acid 57 to Ketone 35



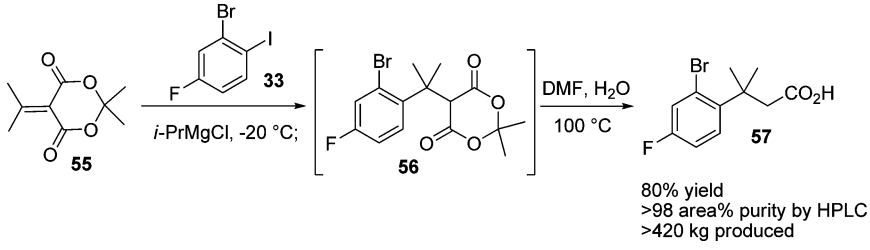
toluene solution was used directly in the next step. The mechanism of the reaction likely proceeds via formation of pyridinium enolate **58**, which is trifluoroacetylated to give **59**. Subsequent addition of water effects hydrolysis to give a *β*-trifluoroacetyl carboxylic acid, which decarboxylates to give the product **35**.

The Meldrum's acid based synthesis of **35** avoided the use of trifluoromethyl enone **28**, removed two product distillations from the synthesis, and employed cheaper reagents. The next challenge was to avoid the use of isocyanate **46** in the preparation of amide ketone **22**. To accomplish this, we performed the same enolization/Grignard exchange reaction, but quenched the intermediate aryl Grignard reagent with CO_2 instead of isocyanate **46** (Scheme 21). This produced the acid/lactol **60a**/**60b** in 78% yield. Compound **60** existed as a ~64:36 mixture of open (**60a**) and closed (**60b**) forms by NMR in *d*-6 DMSO at rt. The acid/lactol **60** was converted to its acid chloride by treatment with $SOCl_2$ in PhMe at 50 °C, and the acid chloride solution was then added to a mixture of 2,6-lutidine and amine **40** to give amide ketone **22** in 75% yield.

With the cost, safety and scalability issues for the synthesis of amide ketone **22** having been addressed in the above second generation synthesis, the next challenge was the development of an asymmetric propargylation of **22**. This was accomplished via the use of propargyl borolane **61**,[32] diethylzinc, and the chiral ligand *N*-isopropyl-L-proline **62** in THF at 20 °C to give a reaction diastereoselectivity of approximately 4:1, from which the desired diastereomer **23** was isolated in 75% yield with a diastereomeric purity of 99:1 after crystallization (Scheme 22). The complete story of the development and scope of this asymmetric propargylation reaction is the subject of the following paper in this journal.[33]

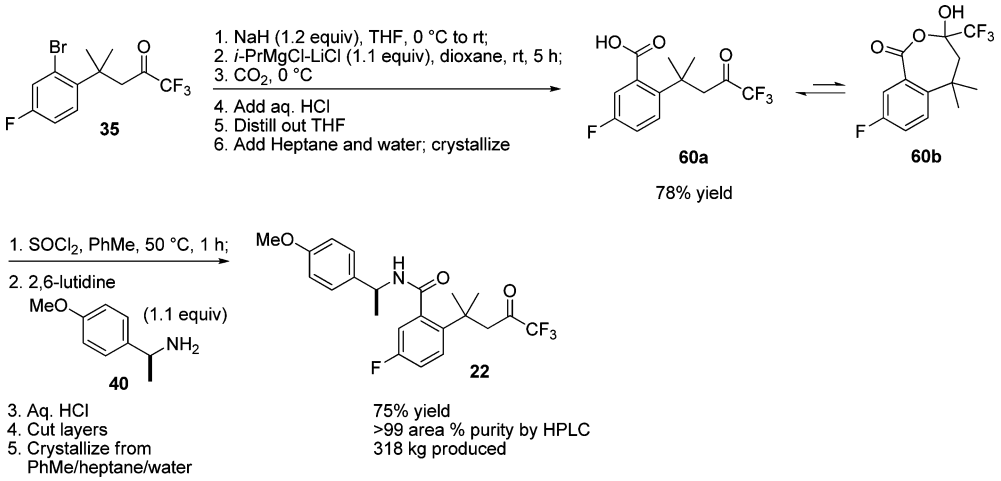
The final issue to be addressed for a large scale process was the amide deprotection step. While the HBr/AcOH procedure was effective, several aspects required improvement. First, the process resulted in the formation of a polymer, poly(4-methoxy)styrene, from the chiral 4-methoxyphenethyl group. This polymer was effectively solubilized by the toluene added during crystallization, but its presence still posed concerns for

Scheme 19. Synthesis of Acid 57

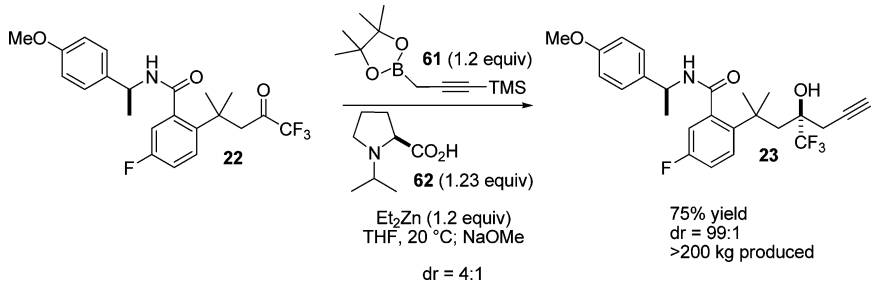


dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

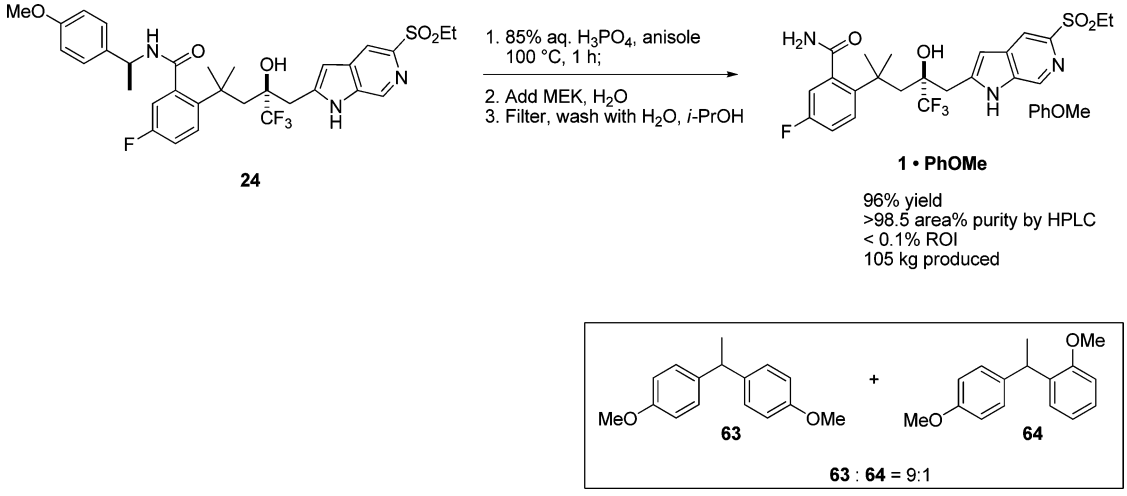
Scheme 21. Synthesis of Amide Ketone 22 via Carboxylation/Coupling



Scheme 22. Asymmetric Propargylation Reaction of 22



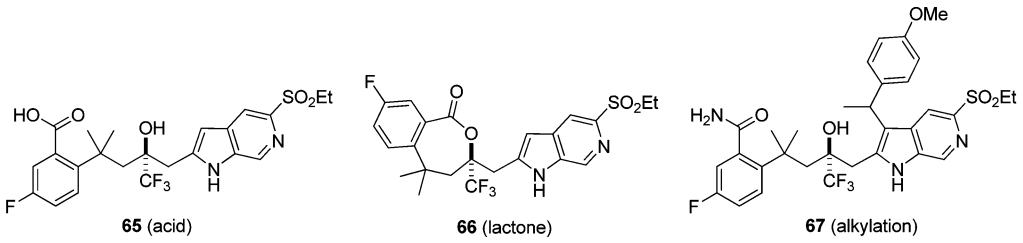
Scheme 23. Deprotection of 24 to 1·PhOMe using H_3PO_4/Anisole



quantification and quality control. Second, the level of impurities formed in the reaction was high, and the need for a recrystallization of the wet cake to achieve adequate purity added to cycle time and decreased the overall yield. Finally, because HBr forms a salt with **1**, addition of an equal amount of NaOH was necessary to neutralize the HBr, and this resulted in a large amount of salt in the reaction which in turn led to a high inorganic content in the isolated product (ROI of up to 0.5%). With these issues in mind, a more extensive screen of reaction conditions was undertaken. The use of anisole as a cosolvent was employed, with the aim of trapping the 4-methoxyphenethyl carbocation and preventing polymer formation. It was found that 85% aqueous H_3PO_4 and anisole at 100 °C for 1 h gave a clean and complete conversion to **1** (Scheme 23). Importantly, the stoichiometric byproducts 1,1-di(4-anisyl)-ethane **63** and the corresponding ortho isomer **64**, formed by trapping of the 4-methoxyphenethyl cation with anisole, were observed in a ∼9:1 ratio. The isolation of the pure para isomer **63** from the reaction in 90% yield indicated that polymer formation was minimal under the reaction conditions. The isolation of the product was accomplished simply by addition of MEK followed by water, which caused direct crystallization of the product as a 1:1 solvate with anisole. Importantly, the higher pK_a of H_3PO_4 (2.15) meant that it did not form a salt

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

Scheme 24. Structures and Levels of Impurities Formed in the Deprotection of 24 to 1·H_3PO_4

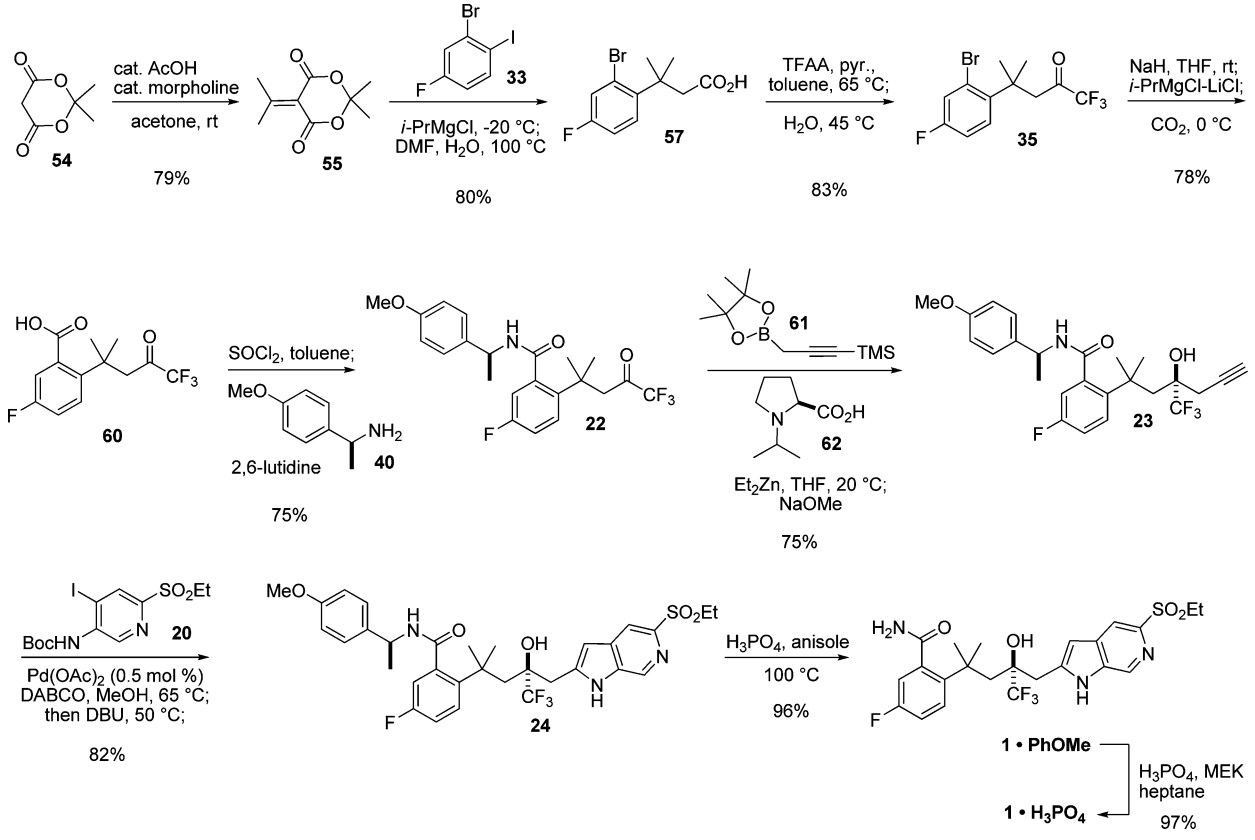


HPLC levels of impurities	HBr/AcOH[a, b]	H_3PO_4/anisole[a]
65 (acid)	0.35%	< 0.05%
66 (lactone)	1.5%	0.2%
67 (alkylation)	2.0%	0.3%

[a]HPLC area% of impurity peak at 220 nm in isolated product.

[b]Levels in solid before recrystallization.

Scheme 25. Second Generation Synthesis of 1·H_3PO_4



with **1** (pK_a = 1.75), and therefore no neutralization was necessary. Consequently, the product did not have any residual inorganic content (ROI <0.1%). After filtration, the product was washed with water and isopropanol. The product **1·PhOMe** was obtained in 96% yield and with a purity of >98.5%. The high purity of the product obtained under these conditions eliminated the need for a recrystallization to upgrade purity.

The major impurities formed in the deprotection reaction are shown in Scheme 24. The acid impurity **65** was formed at a relatively low level with the HBr/AcOH procedure, but proved very difficult to remove by recrystallization. Fortunately, the H_3PO_4/anisole procedure rendered this impurity undetectable. The lactone impurity **66** and the alkylation impurity **67** were formed in large amounts in the HBr/AcOH procedure, but these were also greatly reduced in the H_3PO_4/anisole procedure.

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

The complete second generation synthesis of **1·H_3PO_4** is shown in Scheme 25. The synthesis required 8 chemical steps plus the final cocrystal formation, and proceeded in an overall yield of 17.6%. This was more than double the yield of the first generation synthesis (6.8%), primarily due to the development and implementation of a diastereoselective propargylation reaction. The synthesis addressed the key cost, safety and scalability issues and enabled the production of 94 kg of **1·H_3PO_4** to support development work.

CONCLUSION

In summary, we have described development of a large scale process for the synthesis of glucocorticoid agonist BI 653048 BS H_3PO_4 (**1·H_3PO_4**). The key concept for the route was the propargylation of a trifluoromethyl ketone (**22**) bearing a chiral 4-(methoxyphenyl)ethyl amide to set the tertiary alcohol stereocenter. The bromo trifluoromethyl ketone **35** was prepared initially by a copper catalyzed conjugate addition reaction of an ortho-bromo aryl Grignard reagent to trifluoromethyl enone **28**. Subsequently, a synthesis based on a copper-free conjugate addition of the same aryl Grignard reagent to isopropylidene Meldrum's acid deriviative **55** was employed. The Meldrum's adduct was in situ converted to the corresponding carboxylic acid **57**, which was subsequently converted to trifluoromethyl ketone **35** by a modification of the Zard procedure.[30,31] The amide ketone **22** was prepared by a novel enolization/Grignard exchange/trapping reaction. The highly electrophilic trifluoromethyl ketone was "protected" *in situ* as its sodium enolate, which enabled the functionalization of the aryl bromide into the requisite amide via Grignard exchange and electrophilic trapping, either with an isocyanate, or with carbon dioxide. The propargylation was accomplished initially by deprotonation of trimethylsilylpropyne with *n*-BuLi, transmetalation to $ZnBr_2$, and addition of the resultant allenyl zinc reagent to ketone **22**. While this procedure gave the product with 1:1 diastereoselectivity, the desired diastereomer **23** could be crystallized from the 1:1 mixture in 31−33% yield with a diastereomeric purity of 98:2. Subsequently, a novel diastereoselective version of the propargylation reaction was developed which formed the desired diastereomer in 4:1 selectivity. After crystallization, the desired diastereomer was isolated in 70% yield with a diastereomeric purity of 99:1. The azaindole moiety was introduced by a one-pot Pd-catalyzed cross coupling of iodopyridine **20** with alkyne **23** and subsequent indolization. Finally, the deprotection of the 4-methoxyphenethyl group was effected initially with aqueous HBr and AcOH. Subsequently, an improved procedure using H_3PO_4 and anisole was developed. This process provided the product **1·PhOMe** in high yield and purity, and avoided the formation of polymers from the 4-methoxyphenethyl cation by trapping with anisole to form the discrete adducts **63** and **64**. The phosphoric acid cocrystal final form **1·H_3PO_4** was generated in high yield with consistently small particle size. The diastereoselective propargylation route to **1·H_3PO_4** was employed to prepare >94 kg of drug to support development work and clinical trials.

EXPERIMENTAL SECTION

General Information. All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Melting points are given for crystalline solids and are uncorrected. All ^{1}H and ^{13}C NMR data were referenced to the internal deuterated solvent relative to TMS at 0 ppm. High resolution mass spectroscopy was performed on a TOF instrument with ESI and positive ionization. Flash chromatography was performed on an automated system with silica columns. Compounds **25**−**27**, **30**−**33**, **36**, **39**, **40**, **46**, and **54** are commercially available. The following compounds have previously been described in the literature: **20**,[2] **28**,[1,2,10] **61**,[31a] and **62**.[32]

1,1,1-Trifluoro-4-methylpent-3-en-2-one (28). A reactor was charged with 2-methyl-1-propenylmagnesium bromide **27** (34.75 kg, 36.5 L, 18.25 mol, 1.1 equiv, 0.5 M in THF). The solution was cooled to about −10 °C. *N*-trifluoroacetylmorpholine **26** (3.038 kg, 16.59 mol. 1.0 equiv) was charged at a rate to maintain the batch temperature at not more than 5 °C. The batch was warmed to about 15 °C and held at this temperature for about 1h to complete the addition reaction. The batch was then cooled to about −10 °C and treated with concentrated HCl (4.56 L) at a rate to maintain the batch temperature at not more than 20 °C. Water (13.7 L) and dodecane (7.6 L) were charged and the batch was stirred for 10 min, and then the layers were allowed to settle. The lower aqueous phase was separated. The organic phase was then washed four times with a mixture of water (14.8 L) and MeOH (3.6 L). The organic phase was washed with water (15.2 L), and then was drained from the reactor to yield 9.52 kg of crude product solution, which contained 1.77 kg of **28** by assay (70% yield). This was purified by thin film distillation using a Pope thin-film distillation apparatus. Vacuum of 110−120 mmHg and column set point of 155 °C was used for the first pass. The heavy material obtained after one pass was passed through a second time at a column temperature of 190 °C to drive off the remaining **28**. The receiver flask was cooled in a −50 °C bath to prevent loss of product to the vacuum line. The feed rate of distillate was 3L/hour. A total of 3.35 kg of distillate was obtained which was 49.0 wt% **28**, thus 1.64 kg **28** (65% yield) as a light orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (m, 1 H), 2.24 (d, J = 1.1 Hz, 3 H), 2.02 (d, J = 1.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3 (q, J = 33.6 Hz), 168.5, 116.1 (q, J = 290 Hz), 115.5, 28.4, 21.9.

(*S*)-2-Bromo-5-fluoro-*N*-(1-phenylethyl)benzamide (29). A solution of acid **31** (5.0 g, 22.8 mmol, 1 equiv) in THF (50 mL) was treated portionwise at rt with CDI (4.07 g, 25.1 mmol, 1.1 equiv). The mixture was stirred at rt for 30 min, and then treated with (S)-1-phenylethylamine (3.48 mL, 27.36 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 1h. Water (100 mL) was added, and the mixture was cooled in an ice−water bath. After 1 h, the resultant solid was filtered, washed with water and heptane, and dried under vacuum at 40 °C to give **29** (4.98 g, 68% yield) as a white solid. mp 127−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 7.9 Hz, 1 H), 7.70 (dd, J = 5.2, 8.8 Hz, 1 H), 7.45−7.42 (m, 2 H), 7.37−7.23 (m, 5 H), 5.12 (p, J = 7.2 Hz, 1 H), 1.46 (d, J = 6.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J = 1.7 Hz), 162.2, 159.7, 144.1, 140.8 (d, J = 6.9 Hz), 134.5 (d, J = 8.0 Hz), 128.2, 126.7, 126.1, 117.8 (d, J = 22.4 Hz), 115.9 (d, J = 24.2 Hz), 113.7 (d, J = 3.2 Hz), 48.5, 22.4; HRMS calcd for $C_{15}H_{14}BrFNO$ [M + H]: 322.0237. Found: 322.0214.

4-(2-Bromo-4-fluorophenyl)-1,1,1-trifluoro-4-methylpentan-2-one (35). A reactor was charged with THF (<500 ppm H_2O, 13.40 kg) and 2-bromo-4-fluoro-1-iodobenzene **33** (4.34 kg, 14.4 mol) and the system was flushed with nitrogen. The solution was cooled to −30 °C. *i*-PrMgCl (2.0 M in THF, 7.38 kg, 15.1 mol) was charged to the reactor at a rate to maintain the batch temperature at not more than −25 °C. The reaction mixture was stirred for 30 min at −30 to −25 °C. CuI (274 g, 1.44 mol) was charged as a slurry in THF (1.3 kg) and the reaction was stirred for 15 min at −30 to −25 °C. Then **28** (46.9 wt%, 4.67 kg, 14.4 mol) was charged to the reaction at a rate to maintain the batch temperature at not more than −25 °C. The batch is stirred at −30 to −25 °C for about 10 min, and then warmed to about −20 °C and held at this temperature for about 4 h. A 23 wt% aqueous NH_4Cl solution (26.28 kg) was charged followed by EtOAc (8.57 kg) and the batch was warmed to about 20 °C and stirred at this temperature for at least 4 h. The layers were separated, and the organic phase was washed successively with 23 wt% aqueous NH_4Cl solution (10.26 kg) and 10 wt% aqueous NaCl solution (10.16 kg). The organic phase was distilled to a volume of ∼9 L, discharged, and further distilled under vacuum (6−14 Torr, T_{vap} = 105−123 °C and

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

T_{bath} = 140 − 155 °C) to provide **35** as an orange oil (4.17 kg, 85.6 wt % purity, 75% yield). bp ∼250 °C at 760 Torr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 6.1, 8.9 Hz, 1 H), 7.29 (dd, J = 2.8, 8.2 Hz, 1 H), 7.02−6.97 (m, 1 H), 3.63 (s, 2 H), 1.58 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (q, J = 34.1 Hz), 162.0, 159.5, 139.8 (d, J = 3.7 Hz), 130.2 (d, J = 7.8 Hz), 122.4 (d, J = 24 Hz), 121.1 (d, J = 8.4 Hz), 115.3 (q, J = 290 Hz), 114.3 (d, J = 20.0 Hz), 45.4, 37.8, 28.7. HRMS calcd for $C_{12}H_{10}BrF_4O$ [M − H]: 324.9857. Found: 324.9843.

The following 4 compounds were isolated by chromatography on SiO_2 of nonproduct fractions from the distillation of **35**:

*1-Bromo-3-fluorobenzene (**36**).* Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 2 H), 7.19−7.13 (m, 1 H), 7.00−6.95 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J = 250 Hz), 131.0 (d, J = 8.4 Hz), 127.4 (d, J = 3.1 Hz), 122.7 (d, J = 9.5 Hz), 119.2 (d, J = 24.3 Hz), 114.3 (d, J = 20.8 Hz).

*2-(2-Bromo-4-fluorophenyl)-1,1,1-trifluoro-4-methylpent-3-en-2-ol (**37**).* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 6.3, 9.0 Hz, 1 H), 7.35 (dd, J = 2.6, 8.2 Hz, 1 H), 7.10−7.06 (m, 1 H), 6.04 (s, 1 H), 2.94 (s, 1 H), 1.80 (d, J = 1.4 Hz, 3 H), 1.38 (d, J = 1.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 249 Hz), 141.6, 132.1 (d, J = 8.4 Hz), 122.6, 122.0 (d, J = 24 Hz), 114.2 (d, J = 20 Hz), 76.0 (q, J = 29 Hz), 26.1, 19.1; HRMS calcd for $C_{13}H_{12}BrF_4O_3$ [M + HCO_2]: 370.9911. Found: 370.9897.

*2,2′-Dibromo-4,4′-difluorobiphenyl (**38**).* Waxy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 2.6, 8.4 Hz, 2 H), 7.20 (dd, J = 5.9, 8.2 Hz, 2 H), 7.12−7.07 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 160.8, 137.2 (d, J = 3.7 Hz), 132.1 (d, J = 8.5 Hz), 124.0 (d, J = 9.5 Hz), 119.9 (d, J = 5.8 Hz), 114.5 (d, J = 21.3 Hz). HRMS calcd for $C_{12}H_6BrF_2$ [M − HBr + H]: 266.9615. Found: 266.9603.

*2-Bromo-4-fluorophenol (**39**).* White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.18 (m, 1 H), 6.98−6.91 (m, 2 H), 5.42 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.2, 148.8 (d, J = 2.6 Hz), 118.7 (d, J = 25.9 Hz), 116.4 (d, J = 8.1 Hz), 115.9 (d, J = 22.7 Hz), 109.5 (d, J = 10.2 Hz).

2-(2-(2-Bromo-4-fluorophenyl)-2-methylpropyl)-2-(trifluoromethyl)-1,3-dioxolane (43). To a solution of **35** (3.00 g, 9.17 mmol) in DMF (40 mL) was added 2-chloroethanol (1.84 mL, 27.51 mmol). The reaction mixture was treated with K_2CO_3 (3.80 g, 27.51 mmol) and stirred at rt overnight. The reaction mixture was filtered and the solid washed with EtOAc. The filtrate was concentrated, diluted with EtOAc, and the organic phase washed with water (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give **43** (3.30 g, 87.6 wt% purity, 95% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 6.0, 9.0 Hz, 1 H), 7.33 (dd, J = 2.8, 8.3 Hz, 1 H), 6.96−6.91 (m, 1 H), 3.89−3.79 (m, 2 H), 3.31−3.22 (m, 2 H), 2.71 (br s, 2 H), 1.59 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 159.0, 141.2, 129.6 (d, J = 7.7 Hz), 123.6 (d, J = 8.7 Hz), 123.5 (q, J = 293 Hz), 122.3 (d, J = 23.7 Hz), 113.2 (d, J = 19.4 Hz), 107.0 (q, J = 30.4 Hz), 65.9, 38.0, 30.5; Repeated attempts to obtain HRMS for this compound were unsuccessful.

(*S*)-5-Fluoro-*N*-(1-(4-methoxyphenyl)ethyl)-2-(2-methyl-1-(2-(trifluoromethyl)-1,3-dioxolan-2-yl)propan-2-yl)benzamide (44). A mixture of $Pd(OAc)_2$ (121 mg, 0.54 mmol), BINAP (1.01 g, 1.62 mmol), K_2CO_3 (2.98 g, 21.55 mmol), (*S*)-1-(4-methoxyphenyl)-ethanamine **40** (3.26 g, 21.55 mmol), **43** (4.00 g, 10.78 mmol) and toluene (40 mL) was heated at 110 °C under 250 psi of CO for 20 h. The reaction mixture was filtered through Celite, and the filtrate was washed with 1 M aqueous HCl (50 mL) and water (50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc) to give **44** as a light-brown oil (3.86 g, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 1 H), 7.33−7.29 (m, 2 H), 7.14−7.08 (m, 1 H), 6.98−6.93 (m, 2 H), 6.91−6.87 (m, 2 H), 5.32−5.25 (m, 1 H), 3.91−3.85 (m, 1 H), 3.83−3.77 (m, 1 H), 3.81 (s, 3 H), 3.27−3.21 (m, 1 H), 2.94−2.88 (m, 1 H), 2.46 (d, J = 15.8 Hz, 1 H), 2.24 (d, J = 15.8 Hz, 1 H), 1.56 (d, J = 6.8 Hz, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 161.7, 159.3, 159.0, 140.4 (d, J = 5.9 Hz), 138.2 (d, J = 3.8 Hz), 134.8, 130.1 (d, J = 7.4 Hz), 127.6, 123.2 (q, J = 291 Hz), 115.9 (d, J = 22 Hz), 114.5 (d, J = 20 Hz), 114.1, 107.0 (q, J = 30 Hz), 66.1, 65.8, 55.3, 48.8, 40.9, 36.7, 32.5, 32.0, 21.3; HRMS calcd for $C_{24}H_{28}F_4NO_4$ [M + H]: 470.1949. Found: 470.1922.

(*S*)-5-Fluoro-*N*-(1-(4-methoxyphenyl)ethyl)-2-(5,5,5-trifluoro-2-methyl-4-oxopentan-2-yl)benzamide (22) from 35. A reactor was charged with NaH (0.690 kg, 17.26 mol, 60 wt% in mineral oil) and THF (18.5 L, 500 ppm water). The resultant slurry was cooled to about 0 °C. A solution of **35** (5.25 kg, 14.38 mol, 89.6 wt%) in THF (2.6 L) was added at a rate to control the temperature at not more than 10 °C. The batch was then warmed to about 25 °C and stirred at this temperature for 18 h. Completion of the enolization was confirmed by analysis by IR. The batch was cooled to about 0 °C and treated with *i*-PrMgCl-LiCl (11.66 kg, 1.33 M in THF, 15.82 mol) at a rate that the internal temperature does not exceed 20 °C. 1,4-Dioxane (4.0 L) was charged, and the batch was stirred at about 25 °C for 2−4 h until the bromine/magnesium exchange had reached >99% conversion by GC analysis of aliquots. The batch was cooled to about 0 °C and treated with a solution of isocyanate **46** (2.80 kg, 15.82 mol) in THF (2.6 L) at a rate to control the temperature at not more than 15 °C. The batch was stirred at 5−15 °C for 30 min. A solution of concentrated HCl (5.3 L) in water (15.8 L) was added at a rate to control the temperature at not more than 30 °C. Toluene was charged (10.6 L), the batch was stirred at about 25 °C for 15 min, and the aqueous phase was separated. The organic phase was washed with a solution of NaCl (2.64 kg) in water (21 L). The organic phase was then distilled at about 75 °C under vacuum to a volume of ∼10 L. Toluene (21 L) was charged, and the batch was again distilled at about 75 °C under vacuum to a volume of ∼10 L. Heptane (26 L) was charged at 60−75 °C followed by water (5.3 L). The batch was stirred at about 70−75 °C for 30 min, cooled linearly to 5 °C over 2h, and held at 5 °C for 2h. The batch was filtered, and the solid was washed with heptane (7.5 L). The solid was dried under vacuum with a nitrogen stream at about 50 °C for 12h. **22** was obtained as a white solid (5.33 kg, 97.6 wt% purity, 85% yield). Chiral HPLC (Chiralpak IA column, 225 nm detection, flow rate 1 mL/min, isocratic 90:10 v/v hexanes/*i*-PrOH, 10 min): **22** (7.1 min), 99.9%; enantiomer-**22** (6.2 min), 0.1%; mp 83−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 5.4, 8.9 Hz, 1 H), 7.30−7.24 (m, 2 H), 7.02 (m, 1 H), 6.91−6.86 (m, 3 H), 6.09 (d, J = 7.9 Hz, 1 H), 5.19 (p, J = 6.9 Hz, 1 H), 3.80 (s, 3 H), 3.43 (q, J = 16.6 Hz, 2 H), 1.55 (d, J = 6.9 Hz, 3 H), 1.48 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4 (q, J = 34 Hz), 170.0 (d, J = 1.5 Hz), 161.8, 159.2 (d, J = 25 Hz), 139.7 (d, J = 3.8 Hz), 138.0 (d, J = 5.8 Hz), 134.4, 129.8 (d, J = 7.5 Hz), 127.5, 116.0 (d, J = 20 Hz), 115.5 (d, J = 22 Hz), 115.2 (d, J = 290 Hz), 114.2, 55.3, 49.0, 48.4, 37.4, 29.4, 29.3, 21.2; HRMS calcd for $C_{22}H_{24}F_4NO_3$ [M + H]: 426.1687. Found: 426.1663.

5-Fluoro-2-((*S*)-4-hydroxy-2-methyl-4-(trifluoromethyl)hept-6-yn-2-yl)-*N*-((S)-1-(4-methoxyphenyl)ethyl)benzamide (23). A solution of 1-trimethylsilylpropyne (27.9 mL, 188.4 mmol, 1.6 equiv) and THF (210 mL) was cooled to about −25 °C. *n*-BuLi (70.5 mL, 176.3 mmol, 1.5 equiv, 2.5 M/hexanes) was charged at a rate to control the temperature at not more than −15 °C. The batch was stirred at about −20 °C for about 1 h. A solution of $ZnBr_2$ in THF (116.8 g of 24.9 wt% $ZnBr_2$ in THF, 129.2 mmol, 1.1 equiv) was charged at a rate to control the temperature at not more than −15 °C. The batch was stirred at about −20 °C for about 1 h. A solution of **22** (52.6 g, 95.0 wt%, 117.53 mmol, 1.0 equiv) in THF (105 mL) was charged at a rate to control the temperature at not more than −15 °C. The batch was stirred at about −20 °C for about 1 h. The reaction was then quenched with 3N aqueous HCl (80 mL) at a rate to control the temperature at not more than 20 °C. Additional water (30 mL) was charged. After stirring for about 10 min, the aqueous phase was separated. Water (110 mL) was charged, and after stirring for about 10 min, the aqueous phase was separated. Twenty-five wt% NaOMe in MeOH (79.0 mL, 345.7 mmol, 2.94 equiv) was charged at a rate to control the temperature between 20 and 30 °C. The batch was stirred at about 25 °C for about 1 h. The reaction was then quenched with 3N aqueous HCl (84 mL) at a rate to control the temperature at not more than 30 °C. The pH of the reaction mixture was ∼7. The batch was then distilled under vacuum at up to 70−75 °C to remove THF, MeOH and hexanes. Approximately 415 mL of distillate was collected.

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

i-PrOAc (300 mL) was charged and the batch was cooled to 20−25 °C. The batch was then treated with 3N aqueous HCl (60 mL). After stirring for about 20 min, the aqueous phase was separated. Water (130 mL) was charged, and after stirring for about 10 min, the aqueous phase was separated. The batch was then distilled under vacuum at up to 70−75 °C until 230 mL of distillate was collected. The batch was assayed and adjusted to achieve a concentration of **23** + **49** in *i*-PrOAc of 1g/2.4g. The batch was cooled to about 20−25 °C. Seed crystals of **23** (175 mg) were charged as a slurry in heptane (1 mL), and the batch was stirred for about 30 min at 20−25 °C. Heptane (268 mL) was then added over 1h at 20−25 °C. The batch was stirred for 15h at 20−25 °C and filtered. The solid was washed with 1:3 v/v *i*-PrOAc/heptane (2 × 16 mL), and the solid was dried at 25−35 °C. **23** was obtained as a off-white solid (18.6 g, 97.0 wt% purity, dr = 98.7: 1.3, 33.0% yield). mp 168−169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 5.1, 8.7 Hz, 1 H), 7.31 (d, J = 8.5 Hz, 2 H), 7.05 (ddd, J = 3.1, 8.5, 8.5 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 2 H), 6.84 (dd, J = 3.4, 8.7 Hz, 1 H), 6.10 (d, J = 8.3 Hz, 1 H), 6.05 (s, 1 H), 5.29 (dddd, J = 7.1, 7.1, 7.1, 7.1 Hz, 1 H), 3.82 (s, 3 H), 2.56 (d, J = 15.3 Hz, 1 H), 2.51 (d, J = 18.5 Hz, 1 H), 2.40 (d, J = 17.8 Hz, 1 H), 2.29 (d, J = 15.3 Hz, 1 H), 2.07 (t, J = 2.1 Hz, 1 H), 1.62 (s, 3 H), 1.59 (d, J = 6.8 Hz, 3 H), 1.42 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8 (d, J = 1.8 Hz), 160.5 (d, J = 249 Hz), 159.3, 140.5 (d, J = 3.5 Hz), 137.3 (d, J = 5.8 Hz), 133.9, 130.1 (d, J = 7.6 Hz), 127.5, 125.7 (q, J = 289 Hz), 116.5 (d, J = 19.4 Hz), 115.4 (d, J = 22.6 Hz), 114.3, 78.8, 75.4 (q, J = 26.7 Hz), 71.7, 55.3, 49.1, 42.8, 37.0, 33.3, 33.2, 23.9, 20.64; HRMS calcd for $C_{25}H_{28}F_4NO_3$ [M + H]: 466.2000. Found: 466.2001.

(*S*)-5-Fluoro-2-(4-hydroxy-2-methyl-4-(trifluoromethyl)hept-6-yn-2-yl)benzamide (19) from 23. A solution of amide **23** (2.00 g, 4.30 mmol) in TFA (20 mL) was heated at 50 °C for 16h. The reaction mixture was concentrated, and the residue was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution and water. The organic solution was dried (Na_2SO_4), filtered, and concentrated. Flash column chromatography on SiO_2 (80:20 to 50:50 hexanes/EtOAc) gave pure **19** as an off-white solid (1.14 g, 80% yield). mp 149−151 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 8.37 (s, 1 H), 8.03 (s, 1 H), 7.57 (dd, J = 5.5, 9.0 Hz, 1 H), 7.20 (ddd, J = 2.9, 8.5, 8.5 Hz, 1 H), 7.08 (dd, J = 2.9, 8.8 Hz, 1 H), 6.71 (s, 1 H), 2.86 (br, 1 H), 2.49−2.37 (m, 3 H), 2.32−2.28 (m, 1 H), 1.61 (s, 3 H), 1.46 (s, 3 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 174.6, 160.9, 158.5, 140.2 (d, J = 3.2 Hz), 138.5 (d, J = 6.2 Hz), 130.0 (d, J = 7.4 Hz), 125.9 (q, J = 288 Hz), 115.4 (d, J = 5.5 Hz), 115.2 (d, J = 8.1 Hz), 78.8, 74.9 (q, J = 25 Hz), 73.7, 42.4, 36.9, 32.6, 32.3, 23.7; HRMS calcd for $C_{16}H_{18}F_4NO_2$ [M + H]: 332.1268. Found: 332.1251.

***tert*-Butyl 6-(ethylsulfonyl)-4-iodopyridin-3-ylcarbamate (20).** White solid; mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 8.42 (s, 1 H), 7.02 (br, 1 H), 3.39 (q, J = 7.4 Hz, 2 H), 1.56 (s, 9 H), 1.30 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.8, 140.4, 139.9, 132.7, 98.3, 83.0, 46.8, 28.2, 7.0; HRMS calcd for $C_{12}H_{18}IN_2O_4S$ [M + H]: 413.0027. Found: 413.0003.

2-((*R*)-4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluoro-*N*-((*S*)-1-(4-methoxyphenyl)ethyl)benzamide (24). A reactor was charged with **23** (30.75 kg, 97. Six wt%, 64.45 mol, 1 equiv), **20** (27.6 kg, 97.2 wt%, 65.09 mol, 1.01 equiv), and DABCO (14.82 kg, 132.12 mol, 2 equiv). The vessel was sealed and inerted, and then MeOH (47.5 kg) was charged. A suspension of $Pd(OAc)_2$ (72.0 g, 0.321 mol, 0.005 equiv) in MeOH (4.0 kg) was charged, and the batch was heated at about 65 °C for 3 h to effect complete cross coupling to intermediate **52**. The batch was cooled to about 50 °C, and DBU (14.7 kg, 96.56 mol, 1.5 equiv) was charged at 50−55 °C. The batch was stirred at about 50 °C for about 2 h to effect complete cyclization of **52** to **24**. Acetonitrile (61.3 kg) was charged to the batch at 45−55 °C. Then water (34.5 kg) was charged at 45−55 °C over 30 min. The batch was seeded with **24** seeds crystals (156 g), and held at about 50 °C for 30 min. Water (72 kg) was charged over 1h at about 50 °C, and the batch was cooled over 2 h to about 25 °C, held at this temperature for 1 h, and filtered. The solid was washed with MTBE (198.4 kg) and dried under vacuum at 65 °C with a nitrogen purge for 12 h. **24** was obtained as an off-white solid (36.725 kg, 92.9 wt% purity, 99.4 area% purity by HPLC, 82% yield). Residual Pd: 8.2 ppm. mp 223−225 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 11.63 (s, 1 H), 9.22 (d, J = 7.6 Hz, 1 H), 8.79 (s, 1 H), 8.17 (s, 1 H), 7.60−7.56 (m, 1 H), 7.31 (d, J = 7.6 Hz, 1 H), 7.21−7.15 (m, 1 H), 7.00 (d, J = 8.8 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 2 H), 6.69 (s, 1 H), 6.47 (s, 1 H), 5.10−5.01 (m, 1 H), 3.75 (s, 3 H), 3.37−3.31 (m, 2 H), 3.04 (d, J = 15.6 Hz, 1 H), 2.88 (d, J = 15.6 Hz, 1 H), 2.46 (d, J = 15.6 Hz, 1 H), 2.22 (d, J = 15.6 Hz, 1 H), 1.55 (s, 3 H), 1.44 (d, J = 6.2 Hz, 3 H), 1.36 (s, 3 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 170.3, 160.9, 158.4, 158.1, 144.3, 141.3, 140.8 (d, J = 3.3 Hz), 138.3 (d, J = 5.8 Hz), 135.8, 134.0 (d, J = 6.7 Hz), 131.8, 130.3 (d, J = 7.5 Hz), 127.3, 126.1 (q, J = 289 Hz), 115.7 (d, J = 22 Hz), 115.4 (d, J = 20 Hz), 114.3, 113.6, 102.9, 75.7 (q, J = 25 Hz), 55.1, 48.2, 46.3, 44.8, 37.5, 33.3, 32.8, 30.6, 21.8, 7.0; HRMS calcd for $C_{32}H_{36}F_4N_3O_5S$ [M + H]: 650.2306. Found: 650.2271.

***tert*-Butyl-6-(ethylsulfonyl)-4-((*S*)-6-(4-fluoro-2-((*S*)-1-(4-methoxyphenyl)ethylcarbamoyl)-phenyl)-4-hydroxy-6-methyl-4-(trifluoromethyl)hept-1-ynyl)pyridin-3-ylcarbamate (52).** This intermediate was isolated by extractive workup with EtOAc and water of the above reaction prior to addition of DBU. The organic phase was dried, and the product isolated by chromatography on SiO_2. Tan solid; mp 131−134 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 9.14−9.12 (m, 2 H), 8.55 (s, 1 H), 7.84 (s, 1 H), 7.59 (dd, J = 5.6, 9.0 Hz, 1 H), 7.31−7.27 (m, 2 H), 7.14−7.09 (m, 1 H), 6.91−6.88 (m, 3 H), 6.58 (s, 1 H), 5.02 (p, J = 7.5 Hz, 1 H), 3.74 (s, 3 H), 3.40 (q, J = 7.4 Hz, 2 H), 2.78 (m, 2 H), 2.61 (d, J = 15.3 Hz, 1 H), 2.14 (d, J = 15.3 Hz, 1 H), 1.50 (s, 3 H), 1.46 (s, 9 H), 1.39−1.37 (m, 6 H), 1.13 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 170.1, 160.9, 158.4, 158.1, 151.9, 149.5, 142.0, 140.9 (d, J = 3.4 Hz), 138.8, 138.6 (d, J = 5.8 Hz), 135.8, 130.4 (d, J = 7.2 Hz), 127.3, 124.1, 122.2, 115.5 (d, J = 22 Hz), 115.2 (d, J = 19 Hz), 113.6, 98.5, 81.0, 75.8, 75.1 (q, J = 25 Hz), 55.0, 48.1, 46.1, 43.1, 37.5, 32.8, 30.5, 27.7, 26.8, 25.1, 21.9, 6.7; HRMS calcd for $C_{37}H_{44}F_4N_3O_7S$ [M + H]: 750.2831. Found: 750.2823.

(*R*)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzamide acetic acid solvate (1·AcOH). A reactor was charged with **24** (15.42 kg, 97.19 wt% purity, 23.73 mol, 1 equiv), AcOH (65.2 kg) and 48% aqueous HBr (46.29 kg). The batch was heated at about 80 °C for about 7h. Toluene (64.9 kg) was charged at about 80 °C. The batch was cooled to about 25 °C, and a solution of NaOH (11.0 kg, 275.0 mol) in water (75.0 kg) was added at a rate to control the temperature at not more than 70 °C. The batch was heated to about 75 °C, and a slurry of **1·AcOH** seed crystals (30.0 g) in toluene (1.5 L) was charged. The batch was held at about 75 °C for 30 min, cooled to about 25 °C over 2 h, and held at about 25 °C for 3 h. The batch was filtered, and the solid was washed successively with water (61.8 kg) and toluene (26.7 kg). The wet cake was recharged to a clean reactor. AcOH (35.4 kg) was charged, and the mixture heated to about 75 °C to obtain a solution. Toluene (80.0 kg) was added at 65−75 °C. A slurry of **1·AcOH** seed crystals (15.0 g) in toluene (1.5 L) was charged. The batch was held at about 75 °C for 30 min, cooled to about 25 °C over 2 h, and held at about 25 °C for 1 h. The batch was filtered, and the solid was washed with toluene (26.7 kg). The solid was dried under vacuum at 70 °C with a nitrogen purge for 15 h. **1·AcOH** was obtained as an off-white solid (9.16 kg, 86.6 wt% purity, 98.95 area% purity by HPLC, 67% yield). mp 133−135 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 11.97 (br s, 1 H), 11.59 (s, 1 H), 8.77 (s, 1 H), 8.34 (s, 1 H), 8.15 (s, 1 H), 7.99 (s, 1 H), 7.57 (dd, J = 5.6, 8.9 Hz, 1 H), 7.19−7.11 (m, 2 H), 6.83 (s, 1 H), 6.47 (s, 1 H), 3.34 (q, J = 7.5 Hz, 2 H), 3.05 (d, J = 15.1 Hz, 1 H), 2.93 (d, J = 15.1 Hz, 1 H), 2.49 (d, J = 15.1 Hz, 1 H), 2.34 (d, J = 15.1 Hz, 1 H), 1.92 (s, 3 H), 1.57 (s, 3 H), 1.55 (s, 3 H), 1.07 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 174.2, 172.0, 160.9, 158.5, 144.4, 141.4, 140.2 (d, J = 3.4 Hz), 138.6 (d, J = 5.9 Hz), 134.0 (d, J = 6.2 Hz), 131.8, 130.2 (d, J = 7.4 Hz), 126.1 (q, J = 289 Hz), 115.4 (t, J = 22 Hz), 114.2, 102.8, 75.7 (q, J = 25 Hz), 46.2, 44.6, 37.5, 33.3, 32.6, 31.2, 21.0, 6.9; HRMS calcd for $C_{23}H_{26}F_4N_3O_4S$ [M − AcOH + H]: 516.1575. Found: 516.1547.

(*R*)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-flu-

dx.doi.org/10.1021/jo400079z | *J. Org. Chem.* 2013, 78, 3616−3635

orobenzamide phosphoric acid cocrystal (1·H_3PO_4) from AcOH solvate 1·AcO_3H. A reactor was charged with **1·AcOH** (1.60 kg, 90.5 wt% free base, 2.81 mol, 1 equiv) and MEK (9.6 L). The mixture was heated to about 60 °C to obtain a solution. The warm solution was polish filtered into a clean reactor, using additional warmed (≥40 °C) MEK (3.2 L) to rinse the filter. After adjusting the batch temperature to 50 °C, H_3PO_4 (334.7 g, 2.95 mol, 86.2 wt%, 1.05 equiv) was added at about 50 °C. The batch was stirred for 20 min, and then heptane (2.13 L) was added over about 20 min at about 50 °C. Seed crystals of **1·H_3PO_4** (1.80 g) were added as a slurry in heptane (110 mL). The batch was stirred for 30 min at about 50 °C while a slurry developed. Then heptane (4.27 L) was added over 1h at about 50 °C. The batch was cooled linearly over 2 h to about 20 °C and held at about 20 °C for 2 h. The batch was filtered, and the solid was washed with MEK/heptane 1:2 v/v (2 × 3.3 L) followed by heptane (3.3 L). The solid was dried under vacuum at 70 °C for 24 h. **1·H_3PO_4** was obtained as a white solid (1.61 kg, 99.9 area% purity by HPLC, 93% yield). Chiral HPLC (Chiralpak IA column, 235 nm detection, flow rate 2 mL/min, isocratic 70:30 v/v heptane/*i*-PrOH, 10 min): **1·H_3PO_4** (4.30 min), 99.95%; enantiomer-**22** (3.01 min), 0.05%; mp 204−207 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 11.61 (s, 1 H), 9.58 (br, 3 H), 8.78 (s, 1 H), 8.35 (s, 1 H), 8.16 (s, 1 H), 8.00 (s, 1 H), 7.58 (dd, J = 5.6, 9.0 Hz, 1 H), 7.20−7.12 (m, 2 H), 6.48 (s, 1 H), 3,35 (q, J = 7.6 Hz, 2 H), 3.05 (d, J = 15.0 Hz, 1 H), 2.93 (d, J = 15.0 Hz, 1 H), 2.51 (d, J = 15.0 Hz, 1 H), 2.35 (d, J = 15.0 Hz, 1 H), 1.58 (s, 3 H), 1.55 (s, 3 H), 1.08 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 174.2, 160.9, 158.5, 144.3, 141.4, 140.2 (d, J = 3.7 Hz), 138.6 (d, J = 5.8 Hz), 134.0 (d, J = 5.1 Hz), 131.8, 130.2 (d, J = 7.4 Hz), 126.1 (q, J = 289 Hz), 115.4 (t, J = 22 Hz), 114.3, 102.9, 75.7 (q, J = 25 Hz), 46.2, 44.6, 37.5, 33.3, 32.6, 31.2, 6.9; HRMS calcd for $C_{23}H_{26}F_4N_3O_4S$ [M − H_3PO_4 + H]: 516.1575. Found: 516.1569.

2,2-Dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (55). A reactor was charged with Meldrum's acid **54** (100.0 kg, 693.8 mol, 1 equiv) and acetone (500.0 kg). To the resultant solution was added morpholine (1.05 kg, 12.1 mol, 0.018 equiv) followed by AcOH (0.83 kg, 13.8 mol, 0.02 equiv). The reaction mixture was stirred at about 25 °C for about 48 h. Methylcyclohexane (385 kg) was added, and acetone was distilled out under vacuum at a temperature of not more than 40 °C. MTBE (370 kg) was charged, and the organic phase was washed quickly with 5% aqueous NaOH (2 × 50.0 kg). The organic phase was then distilled under vacuum at not more than 45 °C until the MTBE content was less than 5%. The slurry was cooled to about 0 °C and held at this temperature for about 1 h. The batch was filtered, and the solid washed with cold (0 °C) methylcyclohexane (30.0 kg) and dried under vacuum with a nitrogen stream at 25 °C to give **55** as a white solid (101.0 kg, 79% yield). mp 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 6 H), 1.63 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 161.0, 115.9, 103.5, 27.1, 26.7.

3-(2-Bromo-4-fluorophenyl)-3-methylbutanoic Acid (57). A reactor was charged with 2-bromo-4-fluoro-1-iodobenzene **33** (42.8 kg, 142.2 mol, 1.05 equiv) and THF (50 kg). The solution was cooled to −20 °C and *i*-PrMgCl solution in THF (79.7 kg, 163.5 mol, 1.15 equiv, 2.0 M) was charged at a rate to control the batch temperature at not more than 0 °C. The batch was stirred for 30 min at about −15 °C. A solution of **55** (25.0 kg, 135.7 mol, 1 equiv) in THF (39 kg) was charged at a rate to control the batch temperature at not more than 5 °C. The batch was stirred for 2 h at about 0−10 °C to effect complete conversion to intermediate **56**. The reaction mixture was quenched with a solution of concentrated HCl (25 kg) in water (50 kg) at a rate to control the batch temperature at not more than 25 °C. DMF (55 kg) was charged, and the batch was distilled at atmospheric pressure up to 105 °C to remove THF and toluene. The batch was held at about 105 °C for 15 h. The batch was cooled to about 25 °C and was treated with a solution of concentrated HCl (25 kg) in water (50 kg). The batch was cooled to about 0 °C and held at this temperature for 2 h. The solid was filtered, washed with water (100 kg), and dried under vacuum at about 50 °C until KF ≤ 0.2%. **57** is obtained as an off-white solid (31.0 kg, 96.0 wt% purity, 98.3 area% purity by HPLC, 80% yield). mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (br, 1 H), 7.36 (dd, J = 6.0, 9.0 Hz, 1 H), 7.30 (dd, J = 2.8, 8.3 Hz, 1 H), 6.95−6.91 (m, 1 H), 3.10 (s, 2 H), 1.57 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 160.6 (d, J = 248 Hz), 140.5 (d, J = 3.7 Hz), 129.9 (d, J = 7.8 Hz), 122.6 (d, J = 24 Hz), 121.9 (d, J = 8.6 Hz), 114.0 (d, J = 20 Hz), 44.0, 38.2, 28.7; HRMS calcd for $C_{11}H_{16}BrFNO_2$ [M + NH_4]: 292.0343. Found: 292.0333.

5-(2-(2-Bromo-4-fluorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (56). This compound was isolated from the above procedure by extractive workup with EtOAc and saturated aqueous NH_4Cl after completion of the conjugate addition, and subsequent crystallization from MTBE/hexanes. White solid; mp 116−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 6.1, 9.0 Hz, 1 H), 7.30 (dd, J = 2.8, 8.1 Hz, 1 H), 7.07−7.02 (m, 1 H), 5.61 (s, 1 H), 1.86 (s, 3 H), 1.77 (s, 6 H), 1.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 160.6 (d, J = 249 Hz), 141.1 (d, J = 3.7 Hz), 130.5 (d, J = 7.8 Hz), 122.1 (d, J = 23 Hz), 120.0 (d, J = 8.5 Hz), 114.6 (d, J = 20 Hz), 104.1, 52.0, 40.9, 28.7, 26.4, 25.9, 25.1; HRMS calcd for $C_{15}H_{17}BrFO_4$ [M + H]: 359.0289. Found: 359.0273.

4-(2-Bromo-4-fluorophenyl)-1,1,1-trifluoro-4-methylpentan-2-one (35) from 57. A reactor was charged with **57** (83.6 kg, 303.9 mol, 1 equiv), toluene (295 kg) and TFAA (191 kg, 911.7 mol, 3 equiv). The reaction mixture was cooled to about 0 °C, and pyridine (108 kg, 1367.6 mol, 4.5 equiv) was charged at a rate to control the batch temperature at not more than 35 °C. The reaction mixture was heated to 60−65 °C and held at this temperature for about 12 h. The batch was then cooled to about 5 °C, and water (337 kg) was charged at a rate to control the batch temperature at not more than 50 °C. The reaction mixture is then heated at about 50 °C for about 1h. The reaction mixture was cooled to about 25 °C, and heptane (229 kg) was charged. The aqueous phase was separated, and the batch was washed again with water (334 kg). The batch was then distilled under vacuum at up to 70 °C to remove 434 kg of distillate. After cooling to about 25 °C, the batch was treated with heptane (736 kg) and SiO_2 (50.0 kg), and was agitated for about 30 min. The batch was then filtered, and the SiO_2 cake was washed with heptane (78 kg). The combined filtrates were returned to the cleaned reactor, and were distilled under vacuum at up to 70 °C to remove 876 kg of solvent. The resultant concentrated orange solution of **35** was drained from the reactor and assayed (105.0 kg, 78.7 wt% purity, 83% yield). Spectral data for **35** were consistent with material obtained from conjugate addition to **28**.

5-Fluoro-2-(5,5,5-trifluoro-2-methyl-4-oxopentan-2-yl)-benzoic Acid (60). A reactor was charged with sodium hydride (12.1 kg, 60 wt% in mineral oil, 303.1 mol, 1.2 equiv), THF (184 kg, 300−500 ppm water), and 1,4-dioxane (57 kg), and the slurry was cooled to about 5 °C. A solution of **35** (105.0 kg, 78.7 wt% purity, 252.6 mol, 1 equiv) in THF (63 kg) was charged at a rate to control the evolution of hydrogen gas. The vessel was rinsed with an additional 21 kg of THF. The batch was stirred at about 25 °C for about 2h, at which point IR analysis indicated complete enolization. The reaction mixture was then cooled to about 5 °C, and *i*-PrMgCl-LiCl (213.0 kg, 1.30 M, 290.5 mol, 1.15 equiv) was charged at a rate to control the batch temperature at not more than 20 °C. The batch was stirred at 20−25 °C for 5h to effect complete Br−Mg exchange (monitored by GC of MeOH-quenched aliquots), and was then cooled to about −15 °C. CO_2 gas was bubbled into the reaction mixture (subsurface addition) at a rate to control the batch temperature at not more than 20 °C. A total of 27.5 kg of CO_2 was charged. The reaction mixture was stirred at about 5−15 °C for 30 min. The batch was then cooled to about 0 °C, and a solution of concentrated HCl (103.0 kg) in water (259.0 kg) was charged at a rate to control the batch temperature at not more than 30 °C. The batch was then distilled under vacuum at up to 35 °C to remove 464 kg distillate. Water (207 kg) was then charged to the batch at about 30−35 °C. The batch was cooled to about 0 °C over 2 h, seeded with **60** (70 g), and held at about 0 °C for at least 2 h. The batch was filtered and the solid washed with water (274 kg). The solid was dried under vacuum with a nitrogen stream at 25−30 °C until KF ≤ 0.5%. **60** is obtained as a tan solid (69.6 kg, 82.8 wt% purity, 78% yield). Note: Compound **60** existed as a ∼65:35 mixture of keto-acid **60a** and lactol **60b**, derived from the acid ketalizing with the CF_3 ketone. mp 97−101 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 13.93−13.13 (br s, 0.65 H), 8.51−7.88 (br s, 0.35 H), 7.56−7.47 (m, 1 H),

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

7.41−7.14 (m, 2 H), 3.60 (s, 1.3 H), 2.53−2.49 (m, 0.35 H), 2.18−2.14 (m, 0.35 H), 1.48 (s, 4.95 H), 1.34 (s, 1.05 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 189.6 (q, J = 33 Hz), 171.6, 166.2, 161.7, 161.0, 159.2, 158.6, 140.9, 139.5 (d, J = 3.4 Hz), 135.5 (d, J = 6.5 Hz), 133.8 (d, J = 6.7 Hz), 129.8 (d, J = 7.2 Hz), 127.7 (d, J = 7.0 Hz), 122.0 (q, J = 287 Hz), 118.6 (d, J = 21 Hz), 117.0 (d, J = 24 Hz), 115.9 (d, J = 21 Hz), 115.0 (d, J = 24 Hz), 114.9 (q, J = 291 Hz), 97.9 (q, J = 32 Hz), 47.5, 45.7, 36.5, 35.3, 31.2, 30.2, 28.9; HRMS calcd for $C_{13}H_{16}F_4NO_3$ [M + NH_4]: 310.1061. Found: 310.1052.

(*S*)-5-Fluoro-*N*-(1-(4-methoxyphenyl)ethyl)-2-(5,5,5-trifluoro-2-methyl-4-oxopentan-2-yl)benzamide (22) from 60. A reactor was charged with **60** (64.0 kg, 219.0 mol, 1 equiv) and toluene (258 kg). *N*,*N*-dimethylacetamide (0.14 kg) was added. The slurry was stirred at about 25 °C. Thionyl chloride (28.7 kg, 241.2 mol, 1.1 equiv) was charged and the batch was stirred for 30 min at 25 °C. The reaction mixture was heated at about 50 °C for 3h to effect complete formation of acid chloride. The reaction mixture was then cooled to about 10 °C. In a separate reactor was charged successively *S*-1-(4-methoxy-phenyl)ethylamine (33.2 kg, 175.0 mol, 1.0 equiv), THF (97.4 kg), and 2,6-lutidine (47 kg, 439.3 mol, 2.0 equiv), and the solution was cooled to about 0−5 °C. The acid chloride solution from the first reactor was charged to the second reactor at a rate to control the batch temperature at not more than 10 °C. The reaction mixture was then stirred at about 15−20 °C for 2 h. The batch was cooled to 0−5 °C and quenched with a solution of concentrated HCl (83 kg) in water (280 kg) at a rate to control the batch temperature at not more than 30 °C. The batch temperature was adjusted to about 25 °C, and the aqueous phase was separated. The organic phase was washed with a solution of concentrated HCl (32 kg) and water (64 kg), then with water (2 × 280 kg), and then the organic phase was distilled under vacuum at up to 55 °C until no more distillate comes over. The batch temperature was adjusted to 60−65 °C. Heptane (384 kg) was charged at 60−65 °C followed by water (64 kg), also at 60−65 °C. The batch was cooled linearly over 2 h to 5 °C and held at 5 °C for 1 h. The batch was filtered, and the solid was washed with heptane (10 kg). The solid was dried under vacuum with a nitrogen stream at about 50 °C for 12 h. **22** was obtained as a white solid (70.0 kg, 99.7 wt% purity, 99.7 area% purity, > 99.5% ee, 75.1% yield). Spectral data for **22** were consistent with material obtained from the isocyanate route.

(*R*)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzamide anisole solvate (1·PhOMe). A reactor was charged with **24** (30.00 kg, 92.68 wt% purity, 42.79 mol, 1 equiv), anisole (89.4 kg) and 85% aqueous H_3PO_4 (151.8 kg). The batch was heated at about 100 °C for about 75 min. The batch was then cooled to about 80 °C. MEK (2-butanone, 48.3 kg) was charged at 75−83 °C. Then water (150 kg) was charged over about 1h, while maintaining the batch at 75−83 °C. The batch was held at about 80 °C for 30 min, cooled over about 1h to 20−25 °C, and held at this temperature for about 1h. The batch was then filtered, and the solid was washed with water (90 kg) followed by isopropanol (70.8 kg). The solid was dried under vacuum at about 70 °C with a nitrogen sweep for 16 h, until KF < 0.5%. **1·PhOMe** was obtained as a white solid (26.17 kg, 80.98 wt% free base (excluding anisole weight), 98.7 area% purity by HPLC, 96% yield). mp 194−197 °C; ^{1}H NMR (400 MHz, *d*-6 DMSO) δ 11.59 (s, 1 H), 8.77 (s, 1 H), 8.34 (s, 1 H), 8.15 (s, 1 H), 7.99 (s, 1 H), 7.57 (dd, J = 5.6, 8.9 Hz, 1 H), 7.31−7.27 (m, 1 H), 7.19−7.11 (m, 2 H), 6.94−6.91 (m, 3 H), 6.82 (br, 1 H), 6.47 (s, 1 H), 3.75 (s, 3 H), 3.34 (q, J = 7.3 Hz, 2 H), 3.04 (d, J = 15.0 Hz, 1 H), 2.92 (d, J = 15.0 Hz, 1 H), 2.49 (d, J = 15.0 Hz, 1 H), 2.33 (d, J = 15.0 Hz, 1 H), 1.57 (s, 3 H), 1.55 (s, 3 H), 1.07 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, *d*-6 DMSO) δ 174.2, 160.9, 159.2, 158.5, 144.3, 141.4, 140.2 (d, J = 3.4 Hz), 138.7 (d, J = 5.9 Hz), 134.0 (d, J = 5.8 Hz), 131.8, 130.2 (d, J = 7.4 Hz), 129.4, 126.1 (d, J = 289 Hz), 120.4, 115.4 (t, J = 22 Hz), 114.2, 113.8, 102.8, 75.7 (q, J = 25 Hz), 54.9, 46.2, 44.6, 37.5, 33.2, 32.6, 31.2, 7.0; HRMS calcd for $C_{23}H_{26}F_4N_3O_4S$ [M − PhOMe + H]: 516.1575. Found: 516.1565.

The following 2 byproducts were isolated by chromatography on SiO_2 of a portion of the concentrated organic layer of the mother liquors from the crystallization of **1·PhOMe**.

4,4′-(Ethane-1,1-diyl)bis(methoxybenzene) (63). White solid; mp 67−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−7.09 (m, 4 H), 6.83−6.79 (m, 4 H), 4.04 (q, J = 7.2 Hz, 1 H), 3.75 (s, 6 H), 1.57 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 139.1, 128.5, 113.8, 55.3, 43.2, 22.3; HRMS calcd for $C_{16}H_{22}NO_2$ [M + NH_4]: 260.1645. Found: 260.1639.

1-Methoxy-2-(1-(4-methoxyphenyl)ethyl)benzene (64). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.09 (m, 4 H), 6.89−6.84 (m, 1 H), 6.82−6.77 (m, 3 H), 4.52 (q, J = 7.1 Hz, 1 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 1.54 (d, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 156.9, 138.6, 135.4, 128.7, 127.7, 127.1, 120.6, 113.6, 110.7, 55.5, 55.3, 36.7, 21.2; HRMS calcd for $C_{16}H_{22}NO_2$ [M + NH_4]: 260.1645. Found: 260.1637.

The following 3 impurities were isolated by preparative HPLC of a portion of the concentrated organic layer of the mother liquors from the crystallization of **1·PhOMe**.

(*R*)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzoic acid (65). White solid; ^{1}H NMR (600 MHz, *d*-6 DMSO) δ 13.58 (br, 1 H), 11.64 (s, 1 H), 8.76 (s, 1 H), 8.12 (s, 1 H), 7.58 (dd, J = 5.6, 9.1 Hz, 1 H), 7.22−7.19 (m, 1 H), 7.18−7.16 (m, 1 H), 6.42 (s, 1 H), 6.17 (br, 1 H), 3.35−3.31 (m, 2 H), 2.87 (d, J = 15.2 Hz, 1 H), 2.71 (d, J = 15.6 Hz, 1 H), 2.64 (d, J = 15.2 Hz, 1 H), 2.18 (d, J = 15.2 Hz, 1 H), 1.63 (s, 3 H), 1.44 (s, 3 H), 1.06 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, *d*-6 DMSO) δ 171.8, 170.2, 160.5, 158.8, 144.4, 141.0, 140.9, 136.1, 133.9, 131.8, 130.1 (d, J = 7.7 Hz), 126.1 (q, J = 287 Hz), 115.9 (d, J = 20 Hz), 115.0 (d, J = 22 Hz), 114.2, 102.8, 75.8 (q, J = 25 Hz), 59.7, 46.2, 44.1, 37.9, 33.0, 32.6, 29.3, 20.7, 14.0, 6.9; HRMS calcd for $C_{23}H_{25}F_4N_2O_5S$ [M + H]: 517.1420. Found: 517.1411.

(*R*)-3-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-8-fluoro-5,5-dimethyl-3-(trifluoromethyl)-4,5-dihydrobenzo[c]oxepin-1(3H)-one (66). White solid; ^{1}H NMR (600 MHz, *d*-6 DMSO) δ 12.06 (s, 1 H), 8.75 (s, 1 H), 8.19 (s, 1 H), 7.49 (dd, J = 3.5, 6.0 Hz, 1 H), 7.37 (ddd, J = 2.9, 2.9, 8.3 Hz, 1 H), 7.20 (dd, J = 2.9, 8.9 Hz, 1 H), 6.53 (s, 1 H), 3.35 (q, J = 7.5 Hz, 2 H), 3.27 (d, J = 15.5 Hz, 1 H), 3.14 (d, J = 15.8 Hz, 1 H), 2.56−2.50 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.10 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (150 MHz, *d*-6 DMSO) δ 165.9 (d, J = 2.2 Hz), 160.3 (d, J = 245 Hz), 144.8, 141.0 (d, J = 3.3 Hz), 136.9, 134.2, 133.7, 132.0, 131.5 (d, J = 7.2 Hz), 127.7 (d, J = 7.7 Hz), 124.5 (q, J = 283 Hz), 119.8 (d, J = 21 Hz), 117.9 (d, J = 23 Hz), 114.7, 104.5, 81.7 (q, J = 26 Hz), 46.3, 44.1, 36.4, 34.1, 30.6, 30.0, 29.9, 6.8; HRMS calcd for $C_{23}H_{23}F_4N_2O_4S$ [M + H]: 499.1315. Found: 499.1322.

2-((4*R*)-4-((5-(Ethylsulfonyl)-3-(1-(4-methoxyphenyl)ethyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)meth-yl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzamide (67). This compound was formed as an inseparable ∼58:42 mixture of diastereomers. White solid; ^{1}H NMR (600 MHz, *d*-6 DMSO) δ 11.34 (s, 1 H), 8.72−8.71 (m, 1 H), 8.32 (s, 0.58 H, major diast.), 8.26 (s, 0.42 H, minor diast.), 7.98 (s, 0.58 H, major diast.), 7.92 (s, 0.42 H, minor diast.), 7.75 (s, 0.42 H, minor diast.), 7.63 (s, 0.58 H, major diast.), 7.56 (dd, J = 5.6, 8.9 Hz, 0.42 H, minor diast.), 7.52 (dd, J = 5.5, 8.8 Hz, 0.58 H, major diast.), 7.19−6.88 (m, 5 H), 6.84−6.78 (m, 2H), 4.18−4.11 (m, 1 H), 3.71 (s, 1.74 H, major diast.), 3.69 (s, 1.26 H, minor diast.), 3.32−3.20 (m, 2 H), 3.06−2.91 (m, 2 H), 2.58−2.28 (m, 2 H), 1.57−1.47 (m, 9 H), 1.02−0.98 (m, 3 H); ^{13}C NMR (150 MHz, *d*-6 DMSO) δ 174.2, 174.0, 160.6, 160.5, 158.94, 158.90, 157.25, 157.20, 143.5, 139.9, 139.8, 138.8 (d, J = 6.4 Hz), 138.6 (d, J = 5.5 Hz), 137.2, 137.0, 136.6, 134.22, 134.17, 133.8, 133.7, 130.2, 130.1, 130.0, 129.6, 129.4, 127.8, 127.7, 126.1 (q, J = 287 Hz), 119.0, 118.9, 115.5, 115.4, 115.3, 115.1, 113.5, 113.43, 113.40, 76.0, 54.9, 48.5, 46.1, 45.5, 45.4, 37.4, 37.3, 33.5, 33.2, 33.0, 31.5, 31.0, 30.4, 30.3, 20.1, 6.7; HRMS calcd for $C_{32}H_{36}F_4N_3O_5S$ [M + H]: 650.2312. Found: 650.2319.

(*R*)-2-(4-((5-(Ethylsulfonyl)-1H-pyrrolo[2,3-c]pyridin-2-yl)-methyl)-5,5,5-trifluoro-4-hydroxy-2-methylpentan-2-yl)-5-fluorobenzamide phosphoric acid cocrystal (1•H_3PO_4) from anisole solvate 1·PhOMe. A reactor was charged with **1·PhOMe** (26.10 kg, 80.98 wt% free base, 41.01 mol, 1 equiv) and MEK (138.6 kg). The mixture was heated to about 60 °C to obtain a solution. The warm solution was polish filtered into a clean reactor, using additional

dx.doi.org/10.1021/jo400079z | J. Org. Chem. 2013, 78, 3616−3635

warmed (≥40 °C) MEK (46.2 kg) to rinse the filter. After adjusting the batch temperature to 50 °C, H_3PO_4 (4.91 kg, 43.06 mol, 86.0 wt%, 1.05 equiv) was added at about 50 °C. The batch was treated with heptane (26.1 kg) was added over about 30 min at about 50 °C. Seed crystals of **1·H_3PO_4** (26.0 g) were added as a slurry in heptane (1 L). The batch was stirred for 30 min at about 50 °C while a slurry developed. Then heptane (52.2 kg) was added over 1h at about 50 °C. The batch was cooled linearly over 2 h to about 20 °C and held at about 20 °C for 3 h. The batch was filtered, and the solid was washed with MEK/heptane 1:2 v/v (37.8 kg) followed by heptane (35.8 kg). The solid was dried under vacuum at 80 °C for 24 h. **1·H_3PO_4** was obtained as a white solid (24.4 kg, 99.7 area% purity by HPLC, 99.9% ee, 97% yield). Spectral data for **1·H_3PO_4** were consistent with material obtained starting from **1·AcOH**.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra and X-ray crystallographic data for **1·H_3PO_4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jonathan.reeves@boehringer-ingelheim.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge Professors Erick Carreira, Scott Denmark, Barry Trost, and Peter Wipf for insightful discussions. Dr. Herbert Nar is thanked for performing the X-ray crystal structure analysis of **1·H_3PO_4**. Analytical support provided by Dr. Uwe Zimmermann, Alexandra Backes, Carina Mayer, Irina Peters and Heike Roth is gratefully acknowledged.

■ REFERENCES

(1) (a) Betageri, R.; Gilmore, T.; Kuzmich, D.; Kirrane, T. M.; Bentzien, J.; Wiedenmayer, D.; Bekkali, Y.; Regan, J.; Berry, A.; Latli, B.; Kukulka, A. J.; Fadra, T. N.; Nelson, R. M.; Goldrick, S.; Zuvela-Jelaska, L.; Souza, D.; Pelletier, J.; Dinallo, R.; Panzenbeck, M.; Torcellini, C.; Lee, H.; Pack, E.; Harcken, C.; Nabozny, G.; Thomson, D. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6842. (b) Riether, D.; Harcken, C.; Razavi, H.; Kuzmich, D.; Gilmore, T.; Bentzien, J.; Pack, E. J., Jr.; Souza, D.; Nelson, R. M.; Kukulka, A.; Fadra, T. N.; Zuvela-Jelaska, L.; Pelletier, J.; Dinallo, R.; Panzenbeck, M.; Torcellini, C.; Nabozny, G. H.; Thomson, D. S. *J. Med. Chem.* **2010**, *53*, 6681. (c) Regan, J.; Lee, T. W.; Zindell, R. M.; Bekkali, Y.; Bentzien, J.; Gilmore, T.; Hammach, A.; Kirrane, T. M.; Kukulka, A. J.; Kuzmich, D.; Nelson, R. M.; Proudfoot, J. R.; Ralph, M.; Pelletier, J.; Souza, D.; Zuvela-Jelaska, L.; Nabozny, G.; Thomson, D. S. *J. Med. Chem.* **2006**, *49*, 7887.

(2) Betageri, R.; Bosanac, T.; Burke, M. J.; Harcken, C.; Kim, S.; Kuzmich, D.; Lee, T. W.-H.; Li, Z.; Liu, P.; Lord, J.; Razavi, H.; Reeves, J. T.; Thomson, D. Azaindole Derivatives as Glucocorticoid Mimetics, Their Preparation, Pharmaceutical Compositions, and Uses Thereof. *PCT. Int. Appl.* WO/2009/149139, 2009.

(3) The general synthetic strategy towards **1·H_3PO_4** has been covered by the following provisional patent applications: (a) Fandrick, D. R.; Reeves, J. T.; Song, J. J.; Tan, Z.; Qu, B.; Yee, N.; Rodriguez, S. Process for Preparation of Trifluoromethyl-Substituted Alcohols by Stereoselective Synthesis. *PCT. Int. Appl.* WO/2010/141331, 2010; (b) Fandrick, D. R.; Reeves, J. T.; Song, J. J.; Yee, N. Process for Preparation of Aralkyl Trifluoromethyl Ketones from Meldrum's Acid and Ketones. *PCT. Int. Appl.* WO/2010/141334, 2010; (c) Fandrick, D. R.; Reeves, J. T.; Song, J. J. Process for Stereoselective Synthesis of Alkynyl Aryl Trifluoromethyl Alcohols via Reaction of Silylalkynylboranes with Trifluoromethyl Ketones. *PCT. Int. Appl.* WO/2010/141328, 2010.

(4) Lee, T. W.; Proudfoot, J. R.; Thomson, D. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 654.

(5) Harcken, C.; Ward, Y.; Thomson, D.; Riether, D. *Synlett* **2005**, 3121.

(6) For alternative synthetic approaches to structurally related molecules see: (a) Song, J. J.; Tan, Z.; Xu, J.; Yee, N. K.; Senanayake, C. H. Process for Stereoselective Synthesis of Certain Trifluoromethyl-Substituted Alcohols. *PCT. Int. Appl.* WO/2005/040145, 2005; (b) Song, J. J.; Tan, Z.; Xu, J.; Yee, N. K.; Senanayake, C. H.; Xu, J.; Gallou, F. Stereoselective Synthesis of Certain Trifluoromethyl-Substituted Alcohols. *U.S. Pat. Appl. Publ.* US/2005/0209488, 2005; (c) Song, J. J.; Reeves, J.; Roschangar, F.; Tan, Z.; Yee, N. K. Process for Stereoselective Synthesis of Trifluoromethyl-Substituted Alcohols. *PCT. Int. Appl.* WO/2007/040959, 2007; (d) Reeves, J. T.; Song, J. J.; Tan, Z. Stereoselective Synthesis of Certain Trifluoromethyl-Substituted Alcohols. *PCT. Int. Appl.* WO/2009/134737, 2009.

(7) As of January 9, 2013, 1 gram of (*S*)-(−)-methyl *p*-tolyl sulfoxide (7), catalog # 339997, cost $397.00 from Sigma-Aldrich (http://www.sigmaaldrich.com/catalog/product/aldrich/339997).

(8) Mauragis, M. A.; Veley, M. F.; Lipton, M. F. *Org. Process Res. Dev.* **1997**, *1*, 39.

(9) (a) Paik, S.; Lee, J. Y. *Tetrahedron Lett.* **2006**, *47*, 1813. (b) Chern, C.-Y.; Huang, Y.-P.; Kan, W. M. *Tetrahedron Lett.* **2003**, *44*, 1039. (c) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2000**, 80. (d) James, I. W. *Tetrahedron* **1999**, *55*, 4855.

(10) Henne, A. L.; Hinkamp, P. E. *J. Am. Chem. Soc.* **1954**, *76*, 5147.

(11) Abouabdellah, A.; Bonnet-Delpon, D. *Tetrahedron* **1994**, *50*, 11921.

(12) (a) Boymond, L.; Rottlander, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (b) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(13) (a) Liu, W.; Lei, A. *Tetrahedron Lett.* **2008**, *49*, 610. (b) Surry, D. S.; Su, X.; Fox, D. J.; Franckevicius, V.; Macdonald, S. J. F.; Spring, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 1870.

(14) Walling, C.; Buckler, S. A. *J. Am. Chem. Soc.* **1955**, *77*, 6032.

(15) Initial studies targeted the phenethyl amide, but it was found that the phenethyl group could only be removed using concentrated H_2SO_4, and under these conditions the substrates examined were destroyed. We therefore switched to the 4-methoxyphenethyl group, which can be removed under considerably milder condtions from amides.

(16) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

(17) Bégué, J. P.; Bonnet-Delpon, D. *Tetrahedron* **1991**, *47*, 3207.

(18) (a) Simmons, H. E., Jr.; Wiley, D. W. *J. Am. Chem. Soc.* **1960**, *82*, 2288. (b) Aubert, C.; Begue, J. P.; Charpentier-Morize, M.; Nee, G.; Langlois, B. *J. Fluorine Chem.* **1989**, *44*, 377. (c) Barbasiewicz, M.; Makosza, M. *Org. Lett.* **2006**, *8*, 3745.

(19) Sigurdsson, S. T.; Seeger, B.; Kutzke, U.; Eckstein, F. *J. Org. Chem.* **1996**, *61*, 3883.

(20) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(21) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.

(22) Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

(23) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, *48*, 5041.

(24) $ZnBr_2$ was preferred over $ZnCl_2$ due to the much lower exothermicity of its dissolution in THF. A 26 wt% solution of $ZnBr_2$ in THF was employed.

(25) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.

(26) Kim, S.; Li, Z.; Tseng, Y.-C.; Spinelli, E.; Nar, H.; Varsolona, R.; Reeves, J. T.; Lee, H.; Song, J. J.; Smoliga, J.; Yee, N.; Senanayake, C. *Org. Process Res. Dev.* **2013**, *17*, 540−548.

(27) Vogt, P. F.; Molino, B. F.; Robichaud, A. J. *Synth. Commun.* **2001**, *31*, 679.

(28) Haslego, M. L.; Smith, F. X. *Synth. Commun.* **1980**, *10*, 421.
(29) A more direct approach to **57**, by Friedel–Crafts reaction of 1-bromo-3-fluorobenzene with 3,3-dimethylacrylic acid in the presence of $AlCl_3$ gave predominantly the wrong regioisomer (9:1 regioselectivity favoring alkylation at the position *ortho* to fluorine and *para* to bromine). The same 9:1 regioselectivity was observed in the Friedel–Crafts reaction of 1-bromo-3-fluorobenzene with trifluoromethyl enone **28**.
(30) (a) Reeves, J. T.; Gallou, F.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Tetrahedron Lett.* **2007**, *48*, 189. (b) Reeves, J. T.; Tan, Z.; Fandrick, D. R.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Synth.* **2012**, *89*, 210.
(31) (a) Boivin, J.; El Kaim, L.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 1285. (b) Boivin, J.; El Kaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2573. (c) Boivin, J.; El Kaim, L.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 2585.
(32) (a) Fandrick, D. R.; Roschangar, F.; Kim, C.; Hahm, B. J.; Cha, M. H.; Kim, H. Y.; Yoo, G.; Kim, T.; Reeves, J. T.; Song, J. J.; Tan, Z.; Qu, B.; Haddad, N.; Shen, S.; Grinberg, N.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2012**, *16*, 1131. (b) Fandrick, K. R.; Fandrick, D. R.; Reeves, J. T.; Gao, J.; Ma, S.; Li, W.; Lee, H.; Grinberg, N.; Lu, B. Z.; Senanayake, C. H. *J. Am. Chem. Soc.* **2011**, *133*, 10332. (c) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600.
(33) Fandrick, D. R.; Reeves, J. T.; Bakonyi, J. M.; Nyalapatla, P. R.; Tan, Z.; Niemeier, O.; Akalay, D.; Ollenberger, S.; Fandrick, K. R.; Song, J. J.; Sun, X.; Qu, B.; Haddad, N.; Shen, S.; Ma, S.; Byrne, D.; Chitroda, A.; Fuchs, V.; Narayanan, B. A.; Grinberg, N.; Lee, H.; Yee, N.; Wohlleben, W.; Brenner, M.; Senanayake, C. H. *J. Org. Chem.* **2013**, DOI: jo400080y.