Asymmetric Synthesis

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Concise and Practical Asymmetric Synthesis of a Challenging Atropisomeric HIV Integrase Inhibitor

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Abstract: *A practical and efficient synthesis of a complex chiral atropisomeric HIV integrase inhibitor has been accomplished. The combination of a copper-catalyzed acylation along with the implementation of the BI-DIME ligands for a ligand-controlled Suzuki cross-coupling and an unprecedented bis(trifluoromethane)sulfonamide-catalyzed tert-butylation renders the synthesis of this complex molecule robust, safe, and economical. Furthermore, the overall synthesis was conducted in an asymmetric and diastereoselective fashion with respect to the imbedded atropisomer.*

The acquired immunodeficiency syndrome (AIDS) and the human immunodeficiency virus (HIV) are considered a significant global problem. The advent of multidrug cocktails of different drug classes (highly active antiretroviral therapy) has transformed this disease into what is now considered a treatable chronic infection.[1] Aside from these advances, drug resistance and in particular multidrug resistance are emerging as threats to this therapeutic advancement.[2] Therefore, the advent of new therapeutic approaches is required to keep this disease under control. In the search for new targets for HIV treatment, the integrase enzyme, which catalyzes the insertion of viral DNA into the host genome, is particularly attractive.[3,4] Merck's raltegravir[5] was the first FDA-approved integrase inhibitor (2007). However, resistance mutations have reduced the effectiveness of raltegravir against HIV.[6] An alternate approach is to target the protein–protein interactions of the integrase dimer to stabilize the protein–protein interactions and promote the formation of inactive integrase multimers.[7] In this context, quinoline-based allosteric integrase inhibitors are being investigated to target the LEDGF/p75 binding site.[8,9] Compound **1**[7,10] is in development as a quinoline-based allosteric integrase inhibitor. To support the advancement of this molecule in development, a robust and practical synthesis was required.

The search for increased drug safety and specificity[11] has translated for the most part into increased complexity for drug candidates. Chirality not only imparts additional complexity, but enantiomers generally differ in their biological activity, including toxicity.[12] An emerging element of chirality in drug discovery is atropisomerism,[13] whereby a hindrance of rotation about a specific axis can generate a new element of chirality. In contrast to traditional stereogenic centers, the axially chiral unit can readily interconvert depending on the degree of steric impairment. If the axially chiral element is thermally stable, the drug candidate would then necessitate the synthesis of a single atropisomer, and this was the case for the integrase inhibitor **1** (Figure 1). Owing to the similar complexities of the top quinoline boronate **2** and the lower chiral hydroxy ester quinoline **3**, the most convergent approach would entail a late-stage Suzuki coupling[14] between these two fragments (Scheme 1).[10] Studies determined that the desired atropisomer is the thermodynamically less stable diastereomer,[15] and thus the development of an asymmetric and diastereoselective synthesis was required.

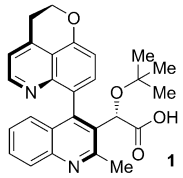

Figure 1. HIV integrase inhibitor **1**.

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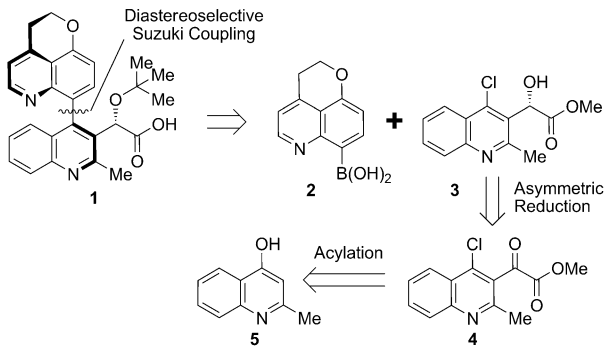


Scheme 1. Retrosynthetic strategy.

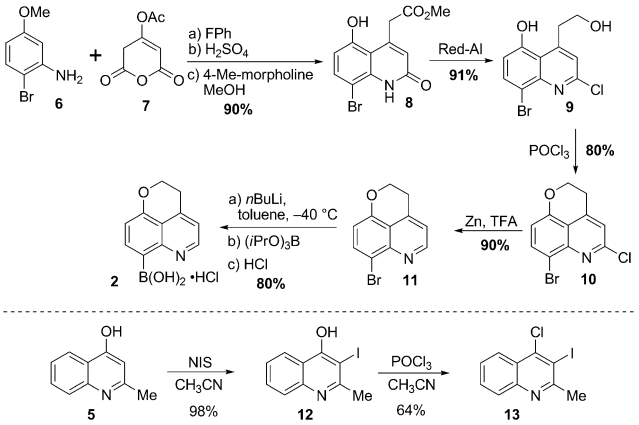


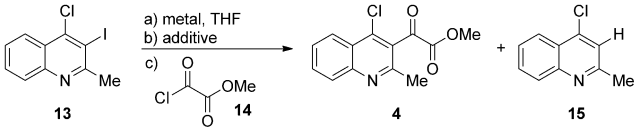
Figure 2. Synthesis of quinoline boronic acid **2** and chloro/iodo-substituted quinoline **13**.

The synthesis of the northern quinoline segment was initiated by the acylation of aniline **6** with unsaturated anhydride **7** (Figure 2). The subsequent intermediate was cyclized by treatment with concentrated sulfuric acid to form 2-oxo-dihydroquinoline **8**. The corresponding ester was reduced with Red-Al to afford diol **9** in 91% yield. After chlorination with $POCl_3$ and in situ cyclization (80% yield), the resulting quinoline chloride was dechlorinated with Zn (90%). A short solvent survey indicated that the lithiation required for the borylation could be efficiently conducted at −40 °C in toluene.[16] Hydrolysis with aqueous HCl formed the desired boronic acid **2**, which was isolated as the HCl salt in 75–80% yield.

Initial studies at the direct Friedel–Crafts-type acylation[17] with hydroxyl-quinoline **5** and methyl oxalyl chloride failed to deliver the desired ketoester. An alternate three-step procedure was developed to supply the necessary substrate. Following the iodination with *N*-iodosuccinimide, the iodo-substituted hydroxyquinoline **12** was found to precipitate directly from the iodination reaction mixture in high yield and purity. The subsequent chlorination with $POCl_3$ provided the substrate for the metal-promoted acylation.

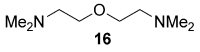
Attempts employing Knochel's magnesium–iodine exchange process[18] with either *i*PrMgCl or *i*PrMgCl·LiCl to generate the Grignard reagent of **13** for the acylation with methyl oxalyl chloride provided the desired ketoester **4** in approximately 50% yield (Table 1). The remaining material was found to be deiodinated quinoline **15**. Attempts to modulate the reactivity of the Grignard reagent with catalytic amounts of $[Fe(acac)_2]$[19] or the use of bis[2-(*N*,*N*-dimethylamino)ethyl] ether (**16**) as a ligand[20] did not offer any improvements. The metalation of the quinoline was shown to be complete as 95% conversion (83% yield) was observed for the corresponding aldehyde in a trapping experiment with DMF. It was postulated that the deiodinated quinoline product could be due to the concurrent deprotonation of the acidic methyl moiety of ketoester product **4**. The corresponding acylated side products arising from the trapping of the deprotonated 2-methyl position were also observed. Although attempts to modulate the reactivity of the metalated quinoline substrate with zinc failed to deliver

Table 1: Acylation studies of iodo-quinoline **14**.[a]



Entry	Reagent	Additive (equiv)	*T* [°C]	Yield **4**[b]	Yield **15**[b]
1	*i*PrMgCl	–	−20 °C to RT	48%	40%
2	*i*PrMgCl	–	−78 °C to RT	50%	50%
3	*i*PrMgCl·LiCl	–	−20 °C to RT	53%	47%
4	*i*PrMgCl	$[Fe(acac)_2]$ (0.1)	−78 °C to RT	28%	72%
5	*i*PrMgCl	**16** (1.2)	−20 °C to RT	29%	71%
6	*i*PrMgCl	$ZnCl_2$ (1.1)	−20 °C to RT	0%	n.d.
7	*i*PrMgCl	$CuBr{\cdot}SMe_2$ (1.1), LiBr (2)	−20 °C to RT	79%	n.d.
8	*i*PrMgCl	CuBr (1.1), LiBr (2)	−20 °C to RT	75%[c]	n.d.
9	*i*PrMgCl	CuBr (0.05)	−20 °C to RT	78%	n.d.

[a] Reactions conducted in THF (5–8 mL of THF/gram of **13**) with methyl chlorooxoacetate (1.2 equiv). [b] Determined by HPLC analysis. [c] Yield of isolated product after crystallization: 68%. acac = acetylacetonate.



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the desired product, the use of copper salts[21] was found to completely suppress the formation of the deiodinated side product **15** and provided the desired ketoester **4** in good yield (75–78%). The effects of the copper salt were found to be preserved even when only catalytic quantities were used (5 mol%, 78% yield).

Whereas attempts at the Corey–Bakshi–Shibata (CBS) reduction[22] of ketoester **4** with the borane/dimethyl sulfide complex proceeded with 30% *ee*, the use of catecholborane[23] increased the enantioselectivity to 94–98% *ee*. This process was initially used to provide material for early development, but owing to the known carcinogenicity of catechol,[24] an alternate asymmetric reduction was required. A ligand survey for the Noyori asymmetric transfer hydrogenation[25] revealed that both *para*-tolyl-substituted ligand **19** and *para*-nitro-substituted **20**[26] were superior in terms of both reaction rates and asymmetric control, providing the desired secondary alcohol in > 90% *ee* (Figure 3). The more reactive *para*-nitro ligand **20** was able to reach complete conversion at more economically viable catalyst levels (600 ppm, Rh dimer). When this system was used at 800 ppm catalyst loading (Rh dimer), the chiral secondary alcohol **3** was isolated in 87% yield and 98% *ee*.

Strategically, the Suzuki–Miyaura cross-coupling was planned with the *tert*-butyl ether on the quinoline halide (quinoline **21**). However, all attempts to deliver the desired atropisomer as the preferred diastereomer failed.[27] It was found that a preference for the desired atropisomer could be realized by employing the unsubstituted hydroxy ester **3** (Figure 4). However, an extensive ligand and condition screen failed to increase the diastereoselectivity to greater than approximately 2:1 favoring the desired atropisomer. Owing to the late-stage coupling of two complex fragments and the low yield of isolated product resulting from this modest

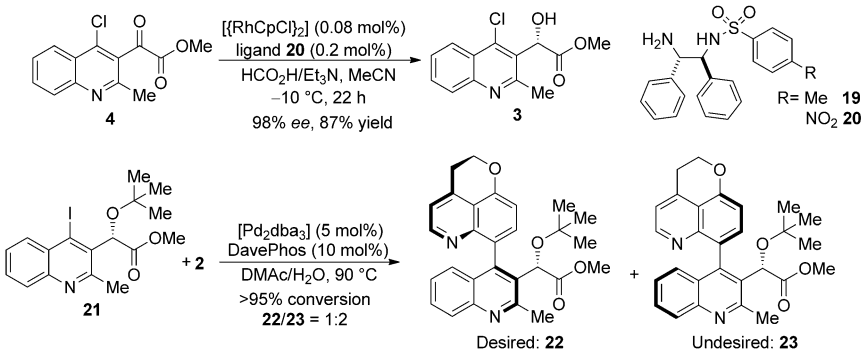


Figure 3. Asymmetric transfer hydrogenation of ketoester **4** and initial attempts at the diastereoselective cross-coupling of **21**. Cp = cyclopentadienyl, dba = dibenzylideneacetone, DMAc = dimethyl acetamide.

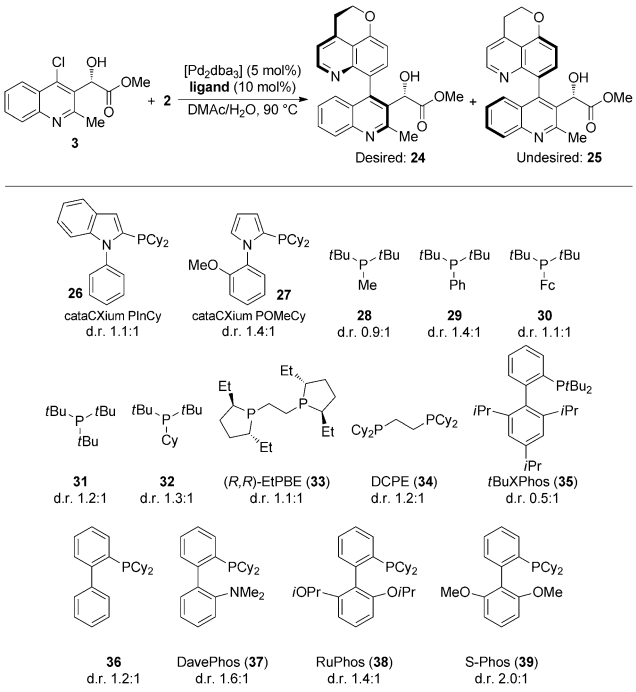


Figure 4. Ligand screen for the Suzuki cross-coupling. The diastereoselectivity (d.r.) is given as the ratio of desired **24**/undesired **25**. Cy = cyclohexyl.

stereocontrol, a diastereoselectivity of 2:1 was deemed economically not viable, and a more selective coupling was required.

Previously, we have shown that the BI-DIME ligands are effective in the asymmetric Suzuki–Miyaura coupling reaction.[28] In this context, we envisioned that the additional chiral control element inherent in the BI-DIME ligands could provide the increase in stereocontrol that was necessary to render the synthesis efficient. A survey of BI-DIME ligands indicated that an electron-rich aromatic ring system was necessary for the coupling (Figure 5). Most of the ligands surveyed favored the desired atropisomer by employing the *S* enantiomer of the respective ligand. Control experiments confirmed that the diastereoselectivity was ligand-controlled, as with the *R* enantiomer of ligand **46**, a complete reversal in atropisomer selectivity was observed, and the racemic ligand **43** provided the atropisomers in equal amounts. Aside from providing a measurable increase in diastereoselectivity, BI-DIME ligand **47** also displayed increased reactivity as compared to the S-Phos ligand. Optimization of the solvent system increased the diastereoselectivity to 5:1 and enabled a reduction of the catalyst loading to 1 mol% (Pd; Figure 6). Notably, the isopropyl substituted BI-DIME ligand (**38**, BI-DIME-*i*Pr)[29] provided a similar selectivity (4.7:1 d.r.) for this challenging cross-coupling. The crystallization of the product **24** increased the atropisomeric ratio to > 95:5, providing the desired diastereomer in 73% yield.

The installation of the *tert*-butyl ether functional group on the bis(quinoline) scaffold of **24** proved to be particularly challenging. Intermediate **24** not only contains two basic quinoline nitrogen atoms, but the *tert*-butyl ether is buried within a sterically crowded environment with the adjacent top quinoline ring system. Attempts to install the *tert*-butyl ether through acid-promoted processes[30] were shown to be not robust as the systems proved to be inherently unstable and would readily revert at ambient temperatures. Jackson's method[31] employing *tert*-butyl trichloroacetimidate **34** was particularly attractive as the system is neutral and would therefore be stable and not prone to reversing. Initial attempts at employing this reagent required large excesses of the neat reagent **49** to reach high conversions (Table 2). It was postulated[32] that the counterion (halides and the triflate anion) could serve a destructive role in the process by competitively trapping the liberated *tert*-butyl cation and catalytically promoting the formation of the isobutylene side product (Figure 7). In this context, it was found that by employing a variety of mild Lewis acidic metals (Mg, Cu, Zn) with the in situ generated hexafluoroantimonate counterion, the number of equivalents of the *tert*-butyl reagent **49** could be reduced to a viable level (5–8) while the reaction was driven to high conversion (up to 90%). Furthermore, a control experiment indicated that silver hexafluoroantimonate itself is competent in the process. Although the catalyst loading could be reduced to 5 mol% by using the $Zn(SbF_6)_2$ system to supply material for short-term needs, an antimony- and metal-free process was required owing to safety and regulatory requirements.

To eliminate the antimony-based counterion, a catalyst formed from the treatment of diethyl zinc with bis(trifluoromethane)sulfonamide was tested in the *tert*-butyl ether formation reaction with **49**, and the reaction was found to perform well (Table 2). Although diethyl zinc failed to promote the etherification, bis(trifluoromethane)sulfonamide itself was competent even at 5 mol% catalyst loading. To render the process cost-effective, *tert*-butyl trichloroacetimidate (**49**) was prepared as a 50 wt%

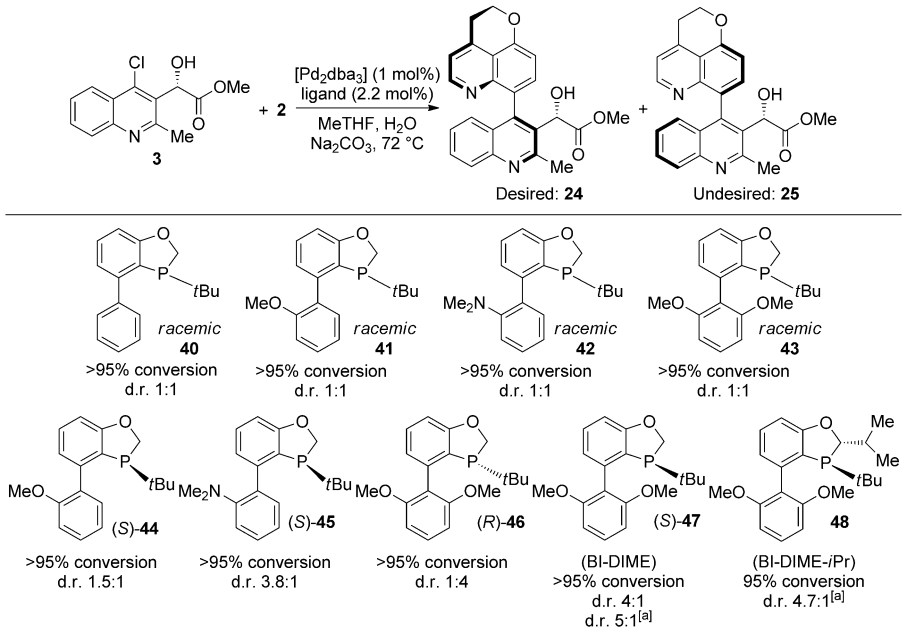


Figure 5. BI-DIME ligand screen for the Suzuki cross-coupling. The diastereoselectivity (d.r.) is given as the ratio of desired **24**/undesired **25**. [a] With 1-pentanol/water as the solvent system instead of THF.

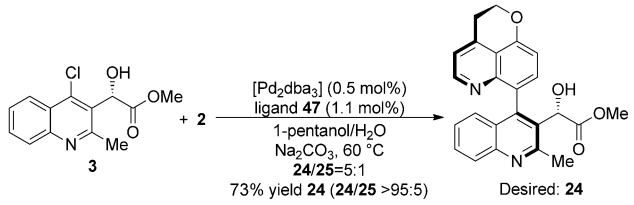


Figure 6. Suzuki cross-coupling between quinoline chloride **3** and boronic acid **2** using BI-DIME ligand **47**.

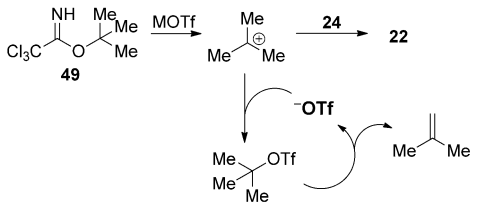


Figure 7. Proposed counterion effect for the *tert*-butylation.

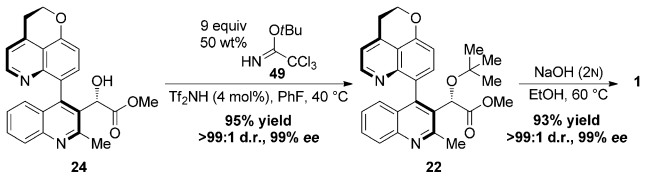
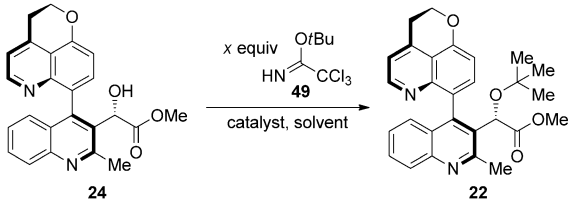


Figure 8. Completion of the synthesis of HIV integrase inhibitor **1**.

solution in fluorobenzene/heptane from relatively inexpensive trichloroacetonitrile and *tert*-butanol and used directly in the etherification. High conversions could be achieved (96%) with nine equivalents of the 50 wt% reagent solution, and the process was shown to be robust and stable at both elevated temperature and with prolonged aging. The process was conducted on a multi-kilogram scale, providing *tert*-butyl ether **22** in 95% yield and >99% d.r. and 99% *ee* after crystallization. The synthesis of the integrase inhibitor was completed by a hydrolysis of the methyl ester to form carboxylic acid **1** (93% yield; Figure 8).

The increasing complexity of compounds in development within the pharmaceutical industry will serve as another avenue of innovation. In this context, the complex atropisomeric integrase inhibitor required multiple elements of methodological development to derive a practical synthesis to supply the necessary material to advance the project forward in development in an economical manner. The combination of the copper-catalyzed acylation along with the implementa-

Table 2: Catalyst survey for the *tert*-butylation of **24**.



Entry	Catalyst (equiv)[a]	Solvent	**38** [equiv]	*T* [°C]	Conv. **22** [%][b]
1	–	DCM	3	RT	0
2	$BF_3{\cdot}OEt_2$ (0.5)	DCM	18	RT	5
3	$Sc(OTf)_3$ (0.5)	DCM	125	RT	82
4	$Cu(OTf)_2$ (0.5)	DCM	18	RT	12
5	$Mg(OTf)_2$ (0.5)	DCM	45	RT	88
6	$Mg(OTf)_2$ (0.5)	DCE	20	43	88
7	$Mg(SbF_6)_2$ (0.25)	DCM	5	RT	75
8	$Cu(SbF_6)_2$ (0.1)	DCE	8	43	88
9	$AgSbF_6$ (0.5)	DCE	8	43	93
10	$Zn(SbF_6)_2$ (0.05)	PhF	6.8	43	87
11	$Zn(Tf_2N)_2$ (0.05)[c]	PhF	5	55	73
12	$ZnEt_2$ (0.05)	PhF	5	55	0
13	Tf_2NH (0.05)	PhF	5	55	75
14	Tf_2NH (0.05)	PhF	9[d]	40	96

[a] The corresponding metal SbF_6 catalysts were prepared from MCl_2 or $MgBr_2$ by treatment with $AgSbF_6$ (2 equiv) followed by filtration before use. [b] Reported as the molar conversion. [c] The $Zn(Tf_2N)_2$ catalyst was prepared by treatment of Et_2Zn with Tf_2NH (2 equiv) in PhF for 15 min before use. [d] Reagent **38** was prepared as a 50 wt% solution in PhF and heptane by treating Cl_3CCN and *t*BuOH in PhF (0.89 mL PhF/mL of Cl_3CCN) with NaO*t*Bu (3 mol%). The solution was diluted with heptane (2.0 mL heptane/mL of Cl_3CCN) and filtered before use. DCE = 1,2-dichloroethane, DCM = dichloromethane, Tf = trifluoromethanesulfonyl.

tion of the BI-DIME ligands and the unprecedented bis(trifluoromethane)sulfonamide-catalyzed *tert*-butylation rendered the synthesis of this complex molecule robust, practical, and economical. Furthermore, the overall synthesis was conducted in an asymmetric and diastereoselective fashion with respect to the imbedded atropisomer. The overall synthesis was shortened to twelve steps, of which the longest linear sequence entailed eight transformations. More importantly, the overall yield was increased to 27% as compared to the unpractical 1.8% from the initial discovery approach.[7] This complex synthesis was conducted on multi-kilogram scale using newly developed innovative processes without any complications.

Keywords: acylation · asymmetric synthesis · phosphine ligands · Suzuki couplings · *tert*-butylation

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