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An Enantioselective Formal Synthesis of Montelukast Sodium

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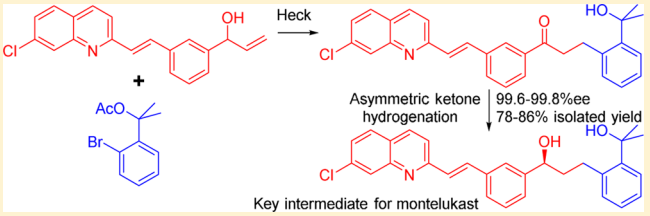
Supporting Information

ABSTRACT: A formal synthesis of the antiasthma drug montelukast sodium is described, wherein the key chiral diol intermediate was accessed with greater convergence of the C−C bond-forming steps as compared to previous routes. Improved synthetic efficiency was achieved by deploying homogeneous metal-based catalysis in two pivotal steps. In the first, a tandem Mizoroki−Heck reaction and double-bond isomerization between a previously known allyl alcohol intermediate and a hindered 2-(2-halophenyl)propan-2-ol secured direct access to the 3-(2-(2-hydroxypropan-2-yl)phenyl)-1-phenylpropan-1-one moiety in the product. In the second step, asymmetric hydrogenation of the ketone functionality in the Mizoroki−Heck reaction product provided a convenient method to introduce the benzylic alcohol chiral center and obtain the desired chiral diol precursor of montelukast sodium. A detailed catalyst screening led to the identification of ((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$ as a catalyst that afforded an enantioselectivity of 99% ee in the hydrogenation step on a multigram lab scale at a molar substrate:catalyst loading of 5000:1.



INTRODUCTION

Developed by Merck Frosst Canada in the 1990s as a part of a drug discovery program to elucidate a selective LTD_4 antagonist, montelukast sodium **1** (Singulair) (Figure 1) is today a widely prescribed medication for the treatment of asthma and symptoms of seasonal allergies.[1] The efforts of Merck Frosst, leading to the discovery and eventual commercialization of Singulair (a once $4.5 billion-a-year drug before the expiry of its patent in 2012), has often been cited as a "*case study in modern drug discovery and development*".[1a] However, there remains scope both to hone existing strategies and to develop novel ones which address shortcomings in known synthetic routes to **1**.

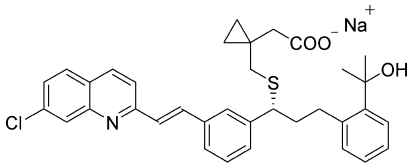


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Figure 1. Structure of montelukast sodium **1**.

A synthetic route generally representative of processes used for **1** is shown in Scheme 1. This employs a Mizoroki−Heck reaction of allylic alcohol **3** with methyl 2-iodobenzoate in a key C−C bond-forming step, followed by asymmetric reduction of ketone **4**. A significant drawback of this approach is the methyl Grignard reagent addition to the aryl ester **5** that leads to the dimethyl aryl carbinol **6**. This requires the use of anhydrous cerium chloride and a large excess of reagent and involves a tedious workup procedure on account of emulsion formation during the solvent extraction process.[2]

We reasoned that the methyl Grignard addition step could be avoided, and additionally a more streamlined overall route realized by employing a halide **10** bearing a preformed dimethyl aryl carbinol moiety in the Mizoroki−Heck reaction step, to provide the key intermediate **9**, from which the diol **6** could be accessed via asymmetric reduction of the ketone functionality (Scheme 2).[3] This reordering, while superficially straightforward, poses significant challenges in both key steps involved. First, the Mizoroki−Heck reaction employs, in place of reactive methyl 2-iodobenzoate, the hindered and less reactive 2-(2-halophenyl)propan-2-ol **10**. Second, a highly enantioselective

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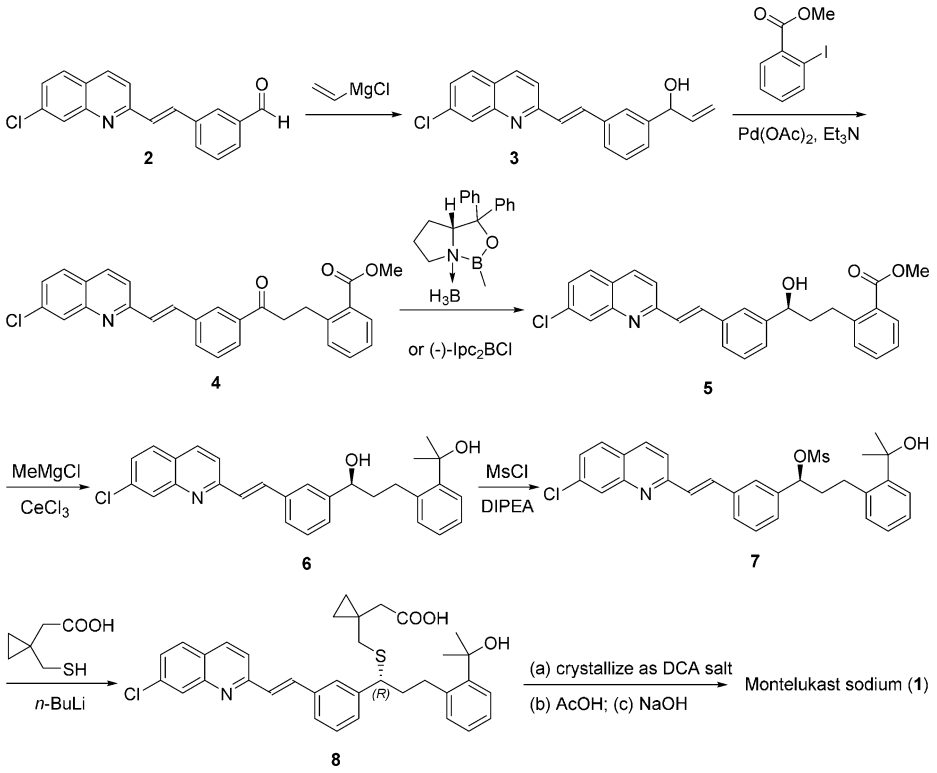
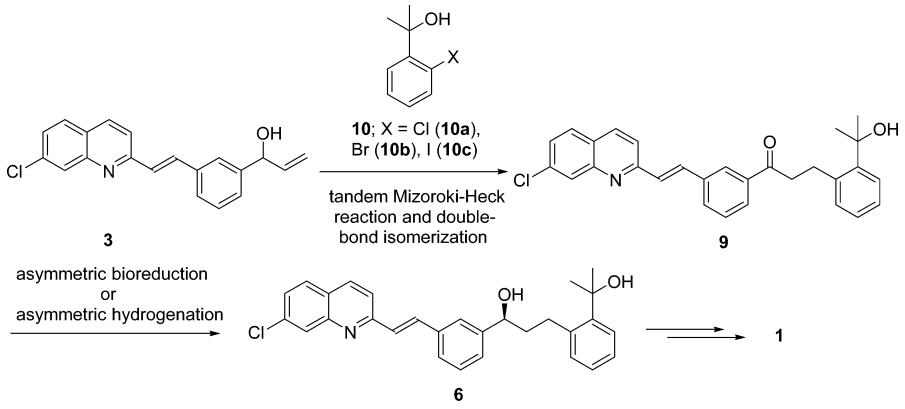
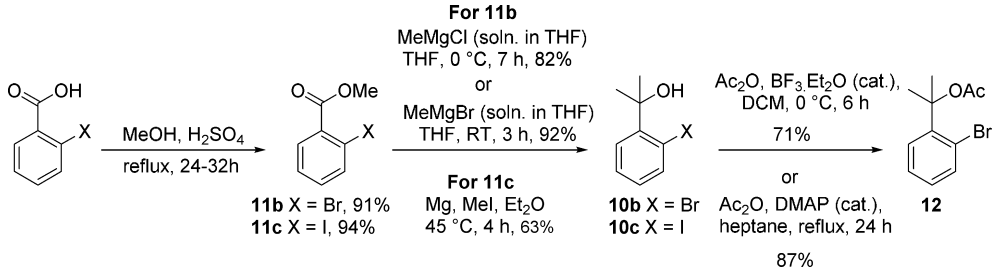
Scheme 1. Known Process Chemistry Route to Montelukast Sodium 1[1a]



Scheme 2. Proposed Formal Synthesis of 1 from the Allyl Alcohol 3 via the Keto-carbinol 9



Scheme 3. Preparation of 2-(2-Halophenyl)propan-2-ols 10 and Acetate 12 from 2-Halobenzoic Acids



and preferably catalytic method of asymmetric reduction of the hindered and functionalized ketone **9** is required.

RESULTS AND DISCUSSION

As outlined, while providing a shorter synthetic route to the keto-carbinol **9**, a direct Mizoroki–Heck coupling[4] between the allyl alcohol **3** and a 2-(2-halophenyl)propan-2-ol **10** presents, as compared to the reaction between **3** and methyl 2-iodobenzoate in the conventional synthesis of **1**, a number of mechanistic hurdles. These are, namely: (a) the presence of the bulky dimethyl carbinol moiety *ortho* to the halogen functionality in the electron-rich halide **10** affecting the rate

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Scheme 4. Mizoroki–Heck Reactions between Allyl Alcohol 3 and Halo-carbinols 10

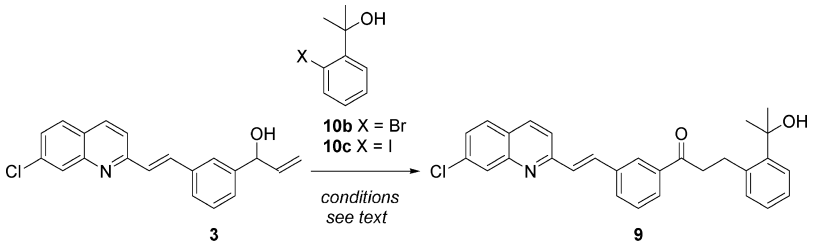
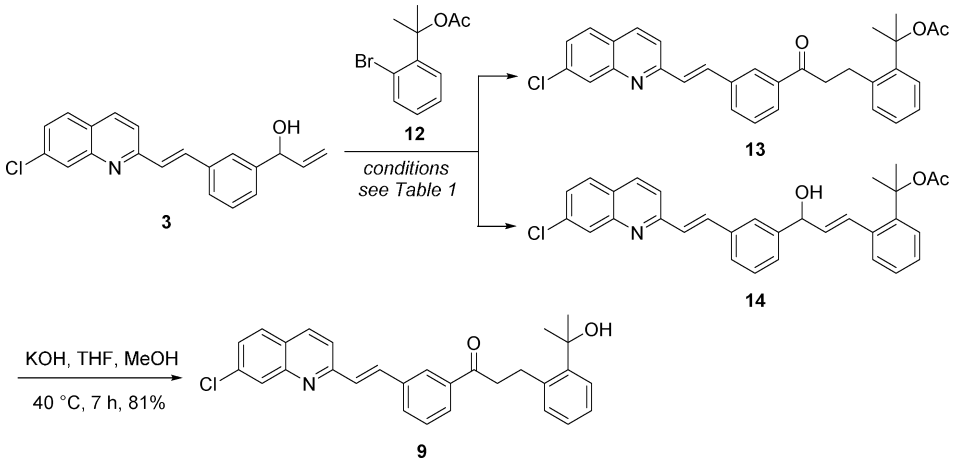


Table 1. Mizoroki–Heck Reaction between the Acetate 12 and the Allyl Alcohol 3

entry	conditions	solvent	temp. (°C)	product ratio (3:13:14)[a]		
1	$Pd(OAc)_2$, LiOAc, TBAB, LiBr, 12 h	DMA	85	NR		
2	$Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, 1.5 days	MeCN	75–80	52	19	29
3	$Pd(OAc)_2$, (*o*-tolyl)$_3$P, DIPEA, 1.5 days	DMA	100–110	3	79	19
4	$Pd(OAc)_2$, (*o*-tolyl)$_3$P, DIPEA, 1.5 days	DMA	120–130	3	81	16

[a]The percentages indicate the proportions of **3**, **13**, and **14** present in the crude reaction mixture, as determined by LC-MS.

Scheme 5. Mizoroki–Heck Reaction between the Acetate 12 and the Allyl Alcohol 3



of oxidative addition; (b) the use of electron-rich phosphine ligands [such as P(*o*-tol)$_3$ or P(*t*-Bu)$_3$] to accelerate the oxidative addition step could slow down the subsequent olefin insertion and reductive elimination steps; and (c) participation of the *tert*-alcohol functionality in **10** in alternate reaction pathways involving Pd insertion across the Ar-(C(CH$_3$)$_2$OH) C–C bond.[5–7]

The requisite tertiary carbinols **10b** and **10c** were conveniently prepared by Fischer–Speier esterification of the 2-halobenzoic acid in the presence of methanol, followed by the addition of excess methyl Grignard reagent to the methyl ester **11**, in the case of **10b**, MeMgBr or MeMgCl, and for **10c**, following a known protocol, MeMgI (Scheme 3).

Efforts to realize the desired Mizoroki–Heck reaction between **3** and bromide **10b** (Scheme 4) met with no success under a variety of conditions, with and without ligands and employing a range of bases and solvents; indeed, no reaction of **10b** was observed even with ethyl acrylate. The bromocarbinol **10b** remained largely unreacted under the conditions tried. With the iodocarbinol **10c**, no reaction occurred using $Pd(OAc)_2/Et_3N$ in refluxing acetonitrile (conditions used commercially for the Mizoroki–Heck reaction between methyl 2-iodobenzoate and **3**). However, the reaction was successful under Jeffery conditions ($Pd(OAc)_2$, LiOAc, *n*-Bu_4NCl, LiCl, DMA). Under these conditions, a loading of down to 0.3 mol % palladium without prior thorough degassing of the reaction solvent was achievable, with an isolated yield of 73%. Use of phosphine ligands in the reaction employing **10c** led to formation of high levels of side products with only partial consumption of **3**. The self-reaction of (2-halophenyl) tertiary carbinols under palladium catalysis is well-documented in the literature,[5–7] and this was not investigated further.

While the use of the iodide **10c** in the Heck–Mizoroki reaction with **3** met our primary objectives, the use of the cheaper bromide remained desirable. With conditions for the free alcohol **10b** proving elusive, we recognized that protection of the 3° hydroxyl group was likely to be necessary, and identified acetate as a group which combined compatibility with the reaction, ease of introduction, and a variety of options for cleavage. Tertiary carbinol **10b** could be esterified with acetic anhydride in the presence of a catalytic amount of either $BF_3 \cdot Et_2O$[8] or more conveniently, DMAP[9] (Scheme 3). The acetate **12** proved to be a reactive partner in the Mizoroki–Heck reaction with allyl alcohol **3**, and in the presence of $Pd(OAc)_2$ and P(*o*-tol)$_3$, the desired acetate-protected keto-carbinol **13** was obtained, *albeit* with varying amounts of an isomeric impurity (Table 1). Although unstable, making isolation and full characterization problematic, from the crude ^{1}H NMR and previous literature precedence, a tentative structural assignment as the allylic alcohol **14** was made.[10]

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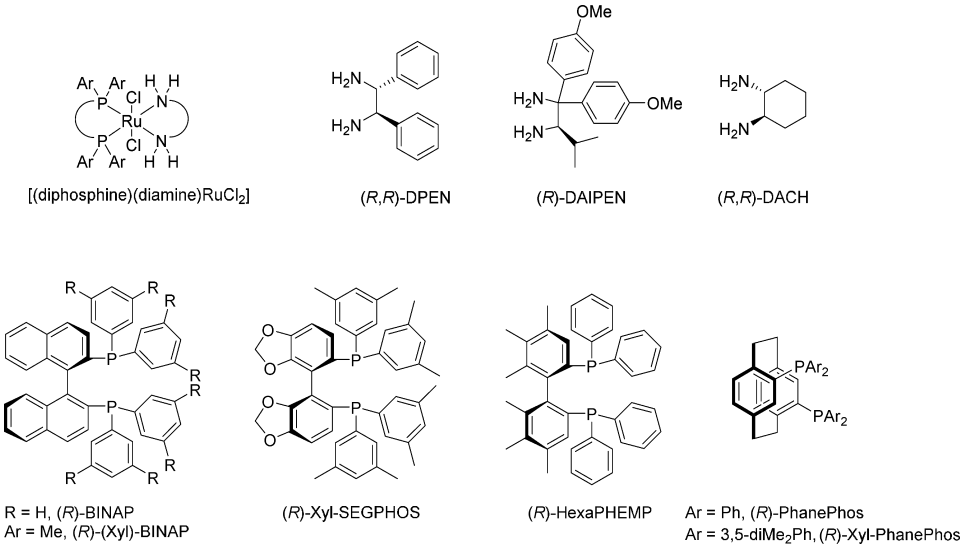

Figure 2. Structures of catalysts and ligands employed in this work.

With subsequent optimization of the reaction conditions using the best ligand/solvent/base combination (Table 1, entry 4) to achieve complete consumption of **3** while minimizing formation of **14**, the Mizoroki−Heck reaction between **3** and **12** provided an isolated yield of 70−76% for the acetate protected keto-carbinol **13**. Warming **13** with KOH in a solvent mixture of THF and MeOH conveniently disengaged the acetate protecting group to furnish the keto-carbinol **9** (Scheme 5).

With the keto-carbinol **9** in hand, we focused our attention toward developing an efficient method for the enantioselective reduction of the ketone group in **9**. Keto-carbinol **9** contains several reducible functionalities, including a disubstituted C═C double bond, an aromatic heterocycle, and an aryl chloride. Hence, in addition to high enantioselectivity, chemoselectivity is required in the asymmetric reduction of **9**. Reported methods for reduction of the related ester-containing keto-ester **4** (Scheme 1) include stoichiometric (−)-chlorodiisopinocampheylborane ((−)-DIP-Cl),[1a,11,12] and catalytic methods employing borane with catalytic CBS,[1a,13] ketoreductase enzymes,[14] asymmetric transfer hydrogenation,[2,15] and asymmetric hydrogenation.[16] Despite providing excellent enantioselectivity, CBS reduction of **4** can lead to a significant over-reduction of the CH═CH to a CH_2-CH_2 linkage in the presence of traces of palladium carried over from the preceding Mizoroki−Heck reaction step.[11] The use of stoichiometric (−)-chlorodiisopinocampheylborane as an alternate chiral reducing agent for this step lowers the possibility of over-reduction, but at increased cost, both of reagents and waste management, and presents additional difficulties such as moisture sensitivity and complex workup.[2] The alcohol functionality in keto-carbinol **9** is also likely to react with the boron-based reagents, resulting in incompatibility or large excesses of reagent being required. We considered enzymatic reduction and catalytic hydrogenation[3,17,18] to be the most attractive methods for asymmetric reduction from the point of view of the use of an economically advantageous reductant (glucose, isopropanol, or hydrogen), achieving economic catalyst loadings and minimization of waste products. In addition, high chemoselectivity is generally achievable with both methods.

Enzymatic reduction of keto-carbinol **9** (Scheme 2)[14] was relatively difficult, with most ADH enzymes screened being inactive. Of commercially available enzymes, KRED-NADH-129[19] was the most active and gave very high enantioselectivity (>99%) in favor of the desired (*S*)-enantiomer. Using glucose as the reductant and GDH for cofactor recycling, a conversion of up to 40% was achievable in aqueous buffer with 5% DMSO cosolvent at a substrate loading of 2.5 g/L. However, with this enzyme, higher conversions were not possible, whether employing higher enzyme concentration, lower substrate concentration or with added cosolvents. In addition to low substrate solubility in the reaction medium, product inhibition of the enzyme is likely to be a significant factor in the incomplete conversion.

Asymmetric hydrogenation of keto-ester **4** has been reported using ruthenium(diamine)(diphosphine) catalysts.[16] However, keto-ester **4** is not stable toward base, which is required for activation of the precatalysts. An approach to minimize the arising detrimental effects of substrate degradation and catalyst deactivation is to employ a biphasic solvent system (chlorobenzene−isopropanol−water) in which base and substrate are partitioned into different phases. An additional benefit of this solvent system is that alcohol **3** forms a stable hemihydrate,[14a] which precipitates from the reaction, protecting it from further base-promoted side reactions such as lactonization.[20] However, a drawback of this approach is that it requires the use of undesirable chlorobenzene.

Illustrative of the constraint of base-instability of keto-ester **4**, if the asymmetric hydrogenation of this compound with [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)$RuCl_2$] (Figure 2) is carried out under conventional reaction conditions with isopropanol as solvent and potassium *tert*-butoxide as base, even at a relatively high catalyst loading (*s*/*c* 500:1), the reaction proceeds rapidly, then stops abruptly within 15 min, with 40% conversion being reached in this example (Figure 3). A significant proportion of the reaction occurred before the 2 min equilibration time of the Biotage Endeavor reactor system used for the experiment. Likewise, base sensitivity of the acetate group in ketone **13**, which was labile in the presence of base and isopropanol, ruled out asymmetric hydrogenation at this stage using ruthenium(diamine)(diphosphine) catalysts, followed by later removal of the acetate group.

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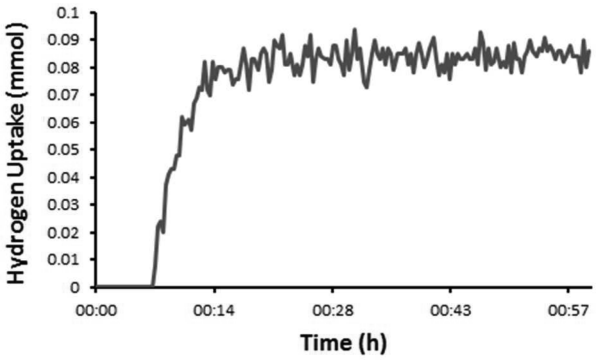

Figure 3. Hydrogen uptake curve for asymmetric hydrogenation of keto-ester **4** with [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)$RuCl_2$] in *i*PrOH with KO*t*Bu as base. Conditions: [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)-$RuCl_2$], 0.55 mmol of substrate, 0.1 equiv of KO*t*Bu, 4 mL of *i*PrOH, 25 °C, 8 bar H_2, *s*/*c* molar 500:1, reaction carried out using Biotage Endeavor.

From the high yield obtained in the final acetate-removal step (Scheme 5), it was clear that keto-carbinol **9**, unlike keto-ester **4**, was stable toward base, providing an advantage in ketone hydrogenation. Keto-carbinol **9** was screened against a range of hydrogenation catalysts (Figure 2, Table 2) under standard reaction conditions employing isopropanol as solvent and potassium *tert*-butoxide as base. Complete conversion was achieved with five catalysts, with the other three giving 50% or higher conversion. Ketone **9** is sparingly soluble in isopropanol, and the reaction proceeds from a slurry to a solution. The complete conversion obtained with keto-carbinol **9** with [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)$RuCl_2$] (entry 5) contrasts with the 40% conversion obtained with keto-ester **4** under these conditions. Three catalysts gave high enantiomeric excesses close to or surpassing 98%, with two, [((*R*)-Xyl-BINAP)-((*R*,*R*)-DPEN)$RuCl_2$] (entry 5) and [((*R*)-Xyl-SEGPHPOS)-((*R*)-DAIPEN)$RuCl_2$] (entry 8), giving over 98.5% enantiomeric excess. With some catalysts, such as [((*S*)-PhanePhos)-((*R*,*R*)-DACH)$RuCl_2$] (entry 2) and [((*R*)-Xyl-SEGPHOS)((*R*,*R*)-DPEN)$RuCl_2$ (entry 7), chemical purity was lower, with significant levels of side reactions occurring. Overall, [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)$RuCl_2$] (entry 5), [((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$] (entry 6), and ((*R*)-Xyl-SEGPHOS)((*R*)-DAIPEN)$RuCl_2$] (entry 8) gave encouraging performance in terms of enantioselectivity, reactivity, and product purity. For this reason, combined with commercial availability, these catalysts were selected for further optimization studies.

Comparison between these catalysts in asymmetric hydrogenation of keto-carbinol **9** was undertaken at lower catalyst loadings, moving toward those required for an economic process. Reactions were carried out in which the reaction profile for uptake of hydrogen with time was determined at *s*/*c* 1000:1 and 2000:1. With [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)-$RuCl_2$], as with ester-containing keto-ester **4**, rapid initial reaction occurred with no detectable induction period (Figure 4). Unlike the reaction with keto-ester **4**, where, under these

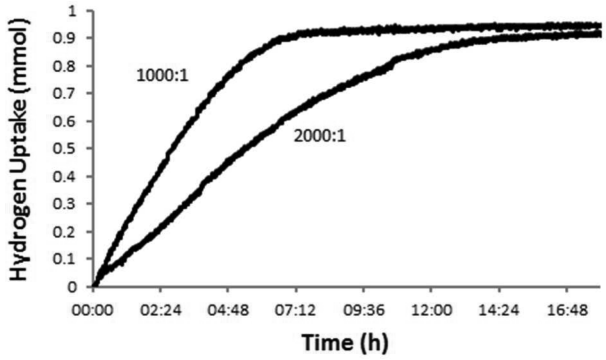

Figure 4. Gas uptake curves for hydrogenation of keto-carbinol **9** with [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)$RuCl_2$] at molar *s*/*c* 1000:1 and 2000:1. Conditions: 1.1 mmol of substrate, 0.1 equiv of KO*t*Bu, 4.8 mL of *i*PrOH, 8 bar H_2, 25 °C 18 h, reactions carried out using Biotage Endeavor.

conditions, abrupt termination of the reaction occurred after a short time, the reaction with keto-carbinol **9** slowed gradually over time, an effect which became more pronounced at lower catalyst loading.

With [((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$], a different reaction profile was obtained (Figure 5) with a pronounced induction period of up to 2 h at 25 °C being apparent. Once the maximum rate was achieved, uptake remained nearly linear until close to the end of the reaction. At 40 °C, the induction period was reduced to 10−15 min. Similar profiles to those shown in Figure 4 were obtained with the other catalysts combining biaryldiphosphine ligands (HexaPHEMP and Xyl-SEGPHOS) and DPEN diamine ligands. The corresponding curves for screening reactions shown in Table 3 with incomplete conversions indicated that these resulted from the reactions being stopped after only 100 min, shortly after the end of the induction period. These biaryldiphosphine/DPEN catalysts, all of which exhibit significant induction periods with keto-carbinol **9**, gave zero conversion when tested against keto-

Table 2. Screening of [(Diphosphine)(diamine)$RuCl_2$] Catalysts for Asymmetric Hydrogenation of Keto-carbinol 9[a,b,c,d]

entry	diphosphine	diamine	conversion (%)[b]	ee (%)[c]
1	(*R*)-HexaPHEMP	(*R*,*R*)-DPEN	50	97.0 (*S*)
2	(*S*)-PhanePhos	(*R*,*R*)-DACH	100	89.6 (*S*)
3	(*R*)-PhanePhos	(*S*,*S*)-DPEN	100	90.7 (*R*)
4	(*S*)-Xyl-PhanePhos	(*R*,*R*)-DPEN	100	71.6 (*S*)
5	(*R*)-Xyl-BINAP	(*R*,*R*)-DPEN	75	98.9 (*S*)
6	(*R*)-Xyl-BINAP	(*R*)-DAIPEN	100	97.9 (*S*)
7	(*R*)-Xyl-SEGPHOS	(*R*,*R*)-DPEN	50	92.2 (*S*)
8	(*R*)-Xyl-SEGPHOS	(*R*)-DAIPEN	100	98.9 (*S*)

[a]Conditions: 0.55 mmol of substrate, 0.1 equiv of KO*t*Bu, 4 mL of *i*PrOH, 8 bar H_2, 25 °C, molar *s*/*c* 500:1. [b]Determined by ^{1}H NMR. [c]Determined by Chiral SFC. For conditions, see the Supporting Information. [d]Catalysts are commercially available from Strem Chemicals, except for entries 1,[17d] 2,[17c] and 3.[17c]

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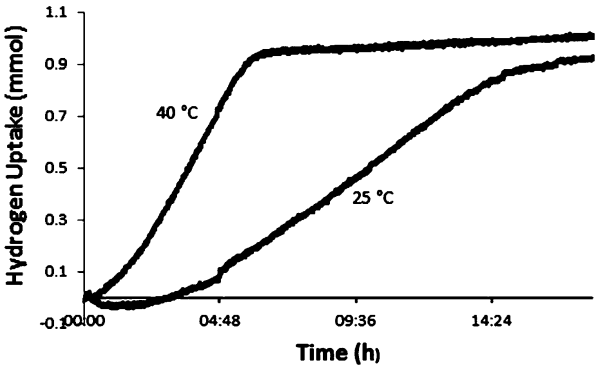

Figure 5. Gas uptake curves for hydrogenation of ketone **9** with ((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$ at 25 and 40 °C. Conditions: 1.9 mmol of substrate, 0.1 equiv of KO*t*Bu, 4.8 mL of *i*PrOH, 8 bar H_2, molar *s*/*c* 1000:1, 18 h, reactions carried out using Biotage Endeavor.

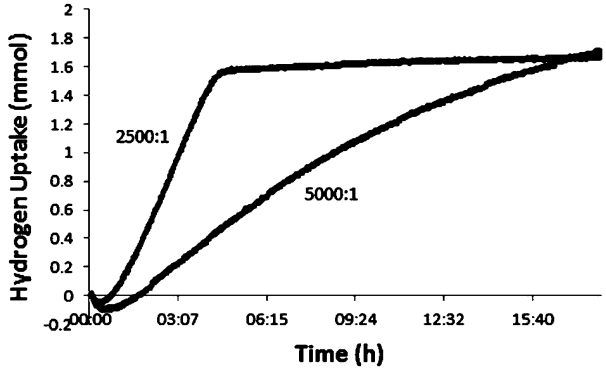

Figure 6. Gas uptake curves for hydrogenation of keto-carbinol **9** with [((*R*)-Xyl-SEGPHOS)((*R*)-DAIPEN)$RuCl_2$] at *s*/*c* 2500:1 and 5000:1. Conditions: 1.1 mmol of substrate, 0.1 equiv of KO*t*Bu, 4.4 mL of *i*PrOH, 8 bar H_2, 40 °C, *s*/*c* 1000:1, 18 h, reaction carried out using Biotage Endeavor.

ester **4** under the *i*PrOH/KO*t*Bu conditions; this may be due to consumption of the base occurring before activation of the catalyst.

Further comparison to determine the optimum catalyst focused on lowering the catalyst loading (Table 3) at higher substrate concentration (200 g/L). With ((*R*)-Xyl-BINAP)-((*R*)-DAIPEN)$RuCl_2$, complete conversion at 25 °C and at 40 °C was achievable down to a loading of 2000:1 with no reduction in enantiomeric excess. Below 2000:1, an erosion in enantiomeric excess was observed, and below 2500:1, conversion was incomplete. The gradual reduction in reaction rate with time and erosion in enantiomeric excess at reduced catalyst loading point to degradation of the catalyst over the course of the reaction, thus limiting the loading achievable with this catalyst. A less pronounced reduction in reaction rate with time and erosion of enantiomeric excess at reduced catalyst loading was apparent with [((*R*)-Xyl-SEGPHOS)((*R*,*R*)-DPEN)$RuCl_2$] (Figure 6). This catalyst also exhibited an induction period, but shorter than that for [((*R*)-Xyl-BINAP)-((*R*,*R*)-DPEN)$RuCl_2$]. A reduction of rate with reaction time and a reduction of enantiomeric excess at lower catalyst loading were not apparent with [((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)-$RuCl_2$], and this catalyst was selected for laboratory scale-up.

The asymmetric hydrogenation of keto-carbinol **9** with [((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$] scaled up well, with a catalyst loading of 5000:1 and enantiomeric excess of 99% being reproducible on a 10−50 g scale. After completion of the reaction, the base was quenched with acetic acid prior to opening the reaction to the atmosphere, in order to avoid formation of strongly colored oxidative catalyst decomposition products which otherwise tended to contaminate the product. The inorganic salts were removed by partitioning between toluene and aqueous sodium carbonate. The crystallization properties of diol **6** were favorable; after recrystallization from isopropanol−heptane or toluene−heptane, the enantiomeric excess of the product increased to 99.6−99.8% in 78−86% yield and a product purity of 99.4−99.6%, the largest impurity being unconverted ketone **9** (0.2−0.3%). The diol **6** was converted to montelukast sodium by known methods.[21] The overall route encapsulating both options for the Mizoroki−Heck reaction is summarized in Scheme 6.

CONCLUSIONS

We describe a concise enantioselective formal synthesis of montelukast sodium **1** via the key chiral diol intermediate **6**, which addresses some of the shortcomings in the conventional synthesis of **1**, most significantly, the late-stage methyl Grignard addition to the methyl ester group, while also achieving a higher degree of convergence. This was achieved by employing metal-based catalysis in two key steps. The first of these, namely, the C−C bond formation in the construction of **9**, was a palladium-

Table 3. Effect of Catalyst Loading in Hydrogenation of Substrate 9 with Three Selected Catalysts[a]

entry	diphosphine	diamine	*s*/*c*	conc. (g/L)	*T* (°C)	conversion (%)[b]	ee (%)[c]
1	(*R*)-Xyl-BINAP	(*R*)-DAIPEN	1000:1	100	25	100	98.8
2	(*R*)-Xyl-BINAP	(*R*)-DAIPEN	2000:1	100	25	100	98.5
3	(*R*)-Xyl-BINAP	(*R*)-DAIPEN	2000:1	100	40	100	98.5
4	(*R*)-Xyl-BINAP	(*R*)-DAIPEN	2500:1	200	40	100	96.9
5	(*R*)-Xyl-BINAP	(*R*)-DAIPEN	5000:1	200	40	60	97.2
6	(*R*)-Xyl-SEGPHOS	(*R*)-DAIPEN	2500:1	200	40	100	98.6
7	(*R*)-Xyl-SEGPHOS	(*R*)-DAIPEN	5000:1	200	40	95	98.5
8	(*R*)-Xyl-BINAP	(*R*)-DPEN	1000:1	100	25	100	98.9
9	(*R*)-Xyl-BINAP	(*R*)-DPEN	1000:1	100	40	100	98.5
10	(*R*)-Xyl-BINAP	(*R*)-DPEN	2000:1	100	40	99	98.9
11	(*R*)-Xyl-BINAP	(*R*)-DPEN	2500:1	200	40	100	98.6
12	(*R*)-Xyl-BINAP	(*R*)-DPEN	5000:1	200	40	100	99.0

[a]Conditions 1.9 mmol of substrate, 0.1 equiv of KO*t*Bu, 4.8 mL of *i*PrOH, 8 bar H_2, 18 h, reactions carried out using Biotage Endeavor. [b]Determined by ^1H NMR. [c]Determined by chiral SFC. For conditions, see the Supporting Information.

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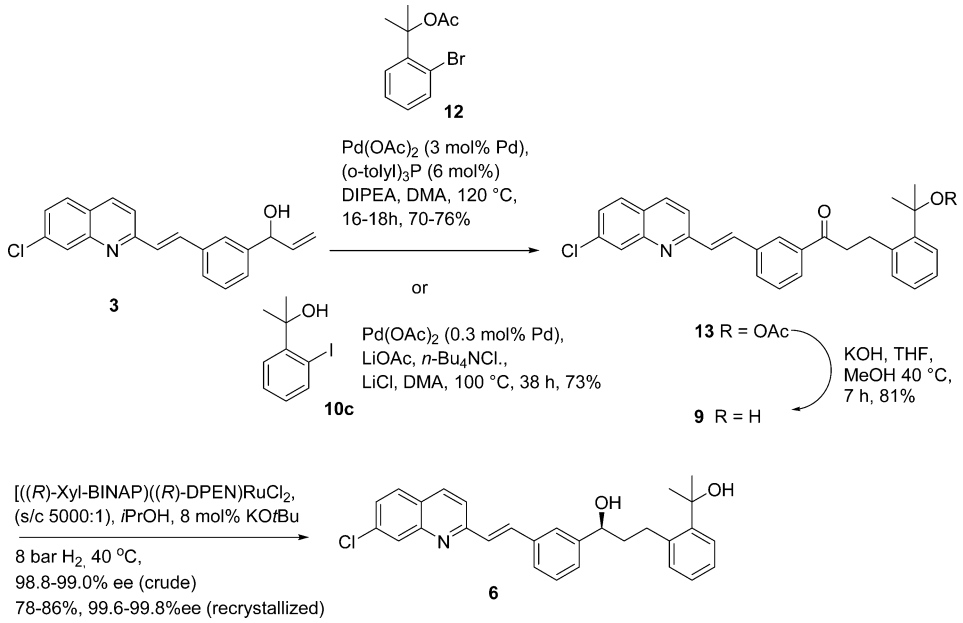
Scheme 6. Overall Scheme for Key Diol Intermediate 6



catalyzed tandem Mizoroki–Heck reaction and double bond isomerization between the allyl alcohol **3** and a sterically hindered dimethyl *o*-halophenyl carbinol, either the free alcohol **10c** in the case of the iodide, or the acetate derivative **11** in the case of the bromide, to furnish the keto-carbinol **9**. With unprotected 2-(2-iodophenyl)propan-2-ol **10c**, the Mizoroki–Heck coupling could be carried out successfully with a palladium loading as low as 0.3 mol % without the need of a phosphine ligand and stringent oxygen-free conditions. Ruthenium-catalyzed asymmetric hydrogenation was employed in the final enantioselective step. Though several of the Ru catalysts screened gave high enantioselectivity and activity under standard monophasic basic reaction conditions, differences in performance between these catalysts became apparent at reduced catalyst loading. With [((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$], it was possible to achieve an enantioselectivity of 99% ee in the reduction of **9** to **6** at a catalyst loading of 5000:1 on a laboratory scale.

EXPERIMENTAL SECTION

Methyl 2-Bromobenzoate (11). The title compound was prepared following a modification of a literature protocol.[22] Thus, 2-bromobenzoic acid (50 g, 0.25 mol) was taken in a dry 500 mL three-neck round-bottom flask, equipped with a stir bar, a reflux condenser, and a calcium chloride guard tube. Methanol (250 mL) was added into the reaction flask, and the mixture thus obtained was stirred at room temperature for 15 min in order to dissolve all solids and obtain a pale yellow clear solution. The reaction mixture was now cooled to 0 °C. Concentrated H_2SO_4 (7.94 mL, 0.15 mol) was added dropwise into the cooled reaction mixture, which was then allowed to reflux for 20 h. Thereafter, the reaction mass was cooled to room temperature and methanol was evaporated completely from the reaction mixture under vacuum. The residue, thus obtained, was neutralized carefully with saturated $NaHCO_3$ solution (100 mL) at 0 °C and then extracted with hexanes (2 × 250 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and passed through a short silica gel, which was then washed with EtOAc. The eluates were concentrated under vacuum to obtain methyl 2-bromobenzoate (51 g, 96% yield, 99% purity from HPLC analysis) as a clear pale yellow liquid, which was pure enough to be employed directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 7.78 (dd, J = 7.6, 1.9 Hz, 1H), 7.66 (dd, J = 7.6, 1.4 Hz, 1H), 7.38–7.30 (m, 2H), 3.93 (s, 1H) ppm.

2-(2-Bromophenyl)propan-2-ol (10b).[23] **(a) Preparation using MeMgBr.** Methyl 2-bromobenzoate (31 g, 0.144 mol) was taken in a dry 1 L three-neck round-bottom flask, equipped with a stir bar, 500 mL dropping funnel, and a nitrogen inlet. The reaction vessel was cooled to 0 °C on an ice bath. MeMgBr (366 mL, 1.18 M solution in THF, 0.432 mol) was added dropwise at 0 °C under nitrogen over a period of 1 h into the stirred reaction mixture. (The actual concentration of the stored MeMgBr reagent (originally purchased as a 1.4 M solution in THF) was estimated by titration against menthol using 1,10–phenanthroline as the end point indicator.) During the course of addition of the Grignard reagent, the reaction mass turned into a clear pale yellow solution. After the addition of the Grignard reagent was complete, the reaction mixture was allowed to stir at 0 °C for an additional 3 h. The reaction mixture gradually turned into a brown colored suspension during this time. After complete consumption of the starting material was indicated by TLC analysis, the reaction mass was quenched at 0 °C with saturated NH_4Cl solution (200 mL). Ethyl acetate (250 mL) was then added, and the reaction mixture was allowed to stir at room temperature for 30 min. The organic layer was then separated, and the aqueous layer was extracted once with ethyl acetate (250 mL). The organic layers were now combined, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue thus obtained was purified by column chromatography using 10% EtOAc–hexanes to obtain 2-(2-bromophenyl)propan-2-ol (28 g, 90% yield, 99% purity from HPLC analysis) as a colorless clear liquid. **(b) Preparation using MeMgCl.** Methyl 2-bromobenzoate (5 g, 0.023 mol) was taken in a dry 100 mL three-neck round-bottom flask, equipped with a stir bar and a nitrogen inlet. The reaction vessel was cooled to 0 °C on an ice bath. MeMgCl (23.3 mL, 3.0 M in THF, 0.069 mol) was added dropwise at 0 °C over a period of 20 min into the stirred reaction mixture. During the addition of the Grignard reagent, the reaction mass turned into an off-white suspension. After the addition of the Grignard reagent was complete, the reaction mixture was allowed to stir at 0 °C. The reaction mixture gradually turned into a sticky mass over a period of 1 h. In order to facilitate the stirring at this stage, dry THF (10 mL) was introduced into the reaction mixture at 0 °C under nitrogen. After the addition of THF, the reaction mixture gradually converted into the same off-white suspension as obtained during the addition of MeMgCl. The reaction mixture was now allowed to stir at 0 °C for an additional 5 h, after which TLC analysis showed complete consumption of the

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starting material and formation of the desired product. The reaction mass was quenched at 0 °C with saturated NH_4Cl solution (25 mL) and then extracted with ethyl acetate (2 × 25 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and evaporated under vacuum to obtain a pale yellow liquid that was purified by column chromatography to obtain 2-(2-bromophenyl)propan-2-ol (4.1 g, 82% yield, 98% purity from HPLC analysis) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 7.67 (dd, J = 7.8, 1.7 Hz, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 7.28 (td, J = 7.8, 1.2 Hz, 1H), 7.08 (td, J = 7.8, 1.7 Hz, 1H), 2.97 (s, 1H), 1.75 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 18 °C) δ = 146.1, 135.1, 133.6, 128.6, 128.0, 127.6, 127.3, 120.5, 73.6, 29.6 ppm.

2-(2-Bromophenyl)propan-2-yl Acetate (12). (a) Preparation using Ac_2O and catalytic BF_3·Et_2O. 2-(2-Bromophenyl)propan-2-ol (2 g, 0.009 mol) was taken in a dry 25 mL round-bottom flask, equipped with a stir bar and a nitrogen inlet. Dry dichloromethane (7 mL), followed by acetic anhydride (1.1 mL, 0.012 mol), was introduced into the reaction flask at room temperature via the standard syringe and septum technique. The resulting reaction mixture was stirred at 0 °C to obtain a colorless clear solution. BF_3·Et_2O (4 drops, ∼2 μL, 1.8 × 10^{-5} mol) was now added to the reaction mixture at 0 °C, which was then stirred at the same temperature for 6 h. Thereafter, the reaction mass was quenched with saturated $NaHCO_3$ solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 15 mL). The organic layers were now combined, dried over anhydrous sodium sulfate, and evaporated under vacuum. The pale yellow liquid thus obtained was purified by column chromatography using 10% EtOAc−hexanes to obtain the acetate **12** (1.7 g, 71% yield, 99% purity from HPLC analysis) as a colorless liquid. **(b) Preparation using Ac_2O and catalytic DMAP.** 2-(2-Bromophenyl)propan-2-ol (27 g, 0.125 mol) was taken in a dry 500 mL three-neck round-bottom flask, equipped with a stir bar, condenser, and a nitrogen inlet. Heptane (285 mL), followed by acetic anhydride (32 g, 0.314 mol) and DMAP (0.459 g, 0.0038 mol), was introduced into the reaction flask at room temperature under a flow of nitrogen. The resulting reaction mixture was stirred and refluxed for 24 h under nitrogen [Note: an additional lot of DMAP (0.460 g, 0.0038 mol) was added into the reaction mixture after 12 h of reflux]. The reaction mixture was then allowed to reflux at 100 °C for an additional 20 h. After TLC analysis showed complete consumption of the starting material, the reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (100 mL). Thereafter, the heptane layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 250 mL). The organic layers were now combined, dried over anhydrous sodium sulfate, and evaporated under vacuum to obtain a brown colored liquid. Purification of this residue by column chromatography afforded the acetate **12** (27 g, 87% yield, 99% purity from HPLC analysis) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 7.67 (dd, J = 7.8, 1.7 Hz, 1H), 7.57 (dd, J = 7.8, 1.2 Hz, 1H), 7.28 (td, J = 7.8, 1.2 Hz, 1H), 7.08 (td, J = 7.8, 1.7 Hz, 1H), 2.97 (s, 1H), 1.75 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 18 °C) δ = 146.1, 135.1, 133.6, 128.6, 128.0, 127.6, 127.3, 120.5, 73.6, 29.6 ppm; HRMS (ES) m/z calcd. for $C_{11}H_{13}BrO_2Na$ $[M + Na]^+$: 278.9997; found 279.0000.

Mizoroki−Heck Reaction between the Acetate 12 and Allyl Alcohol 3: Preparation of (*E*)-2-(2-(3-(3-(2-(7-Chloroquinolin-2-yl)vinyl)phenyl)-3-oxopropyl)phenyl)propan-2-yl Acetate (13). DMA and DIPEA (10 mL) were degassed thoroughly by the freeze−pump−thaw technique. The acetate **12** (7.3 g, 0.0284 mol), allyl alcohol **3** (7.2 g, 0.0224 mol), $Pd(OAc)_2$ trimer (0.146 g, 0.00021 mol), (o-tolyl)$_3$P (0.397 g, 0.0013 mol), and degassed DIPEA (3.514 g, 0.027 mol) were introduced into degassed DMA (100 mL) taken in a dry 250 mL round-bottom flask, equipped with a stir bar, condenser, and a nitrogen inlet. The reaction mixture was stirred at room temperature to dissolve the solids and obtain a clear orange colored solution. The reaction vessel was then dipped into an oil bath heated to 120 °C, and the reaction mass was stirred at the same temperature for 18 h when complete consumption of **3**, as indicated by TLC analysis, was noted. The reaction mass was now cooled to 0 °C, diluted with ice-cold water (500 mL), and stirred for 30 min, whereupon an off-white gummy material precipitated out of the reaction mixture and clung to the walls of the reaction vessel. The aqueous layer was decanted off, and the solid residue was washed with water (100 mL). The aqueous layer and washings were extracted with MTBE (2 × 200 mL). These MTBE extracts and THF (200 mL) were used to dissolve the precipitated gummy material in the reaction vessel. (The gummy residue in the reaction flask was sparingly soluble in MTBE, but dissolved gradually in THF to leave behind a small amount of gray solid.) The solution thus obtained was filtered, and the filtrate was dried over anhydrous sodium sulfate and evaporated under vacuum to obtain 15 g of an off-white solid. The crude material was washed with hexanes, which removed some of the nonpolar impurities. The solid thereafter was made into a slurry in 120 mL of toluene, stirred for 1 h at room temperature, and finally filtered. The residue thus obtained was washed with 50 mL of toluene and dried under vacuum to yield the desired product **13** as a grayish-yellow solid. This was purified further by dissolving it in 1:1 THF−methanol at 50 °C, filtering the solution through a Celite bed to filter the precipitated Pd metal and concentrating the filtrate to obtain 6.6 g of crude **13** as a pale yellow solid. Concentrating the toluene washings and purification of the residue by column chromatography using 30% EtOAc−hexanes afforded an additional 1 g of the desired product **13**. The combined yield of the Mizoroki−Heck reaction product (95% purity from HPLC analysis) was around 70%. ^{1}H NMR (400 MHz, DMSO-d6, 18 °C) δ = 8.41 (d, J = 8.8 Hz, 1H), 8.36 (s, 1H), 8.06−7.86 (m, 6H), 7.65−7.56 (m, 3H), 7.43−7.37 (m, 1H), 7.35 (dd, J = 7.8, 1.0 Hz, 1H), 7.27−7.21 (m, 1H), 7.21−7.14 (m, 1H), 3.52−3.37 (m, 2H), 3.27−3.08 (m, 2H), 1.91 (s, 3H), 1.78 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 18 °C) δ = 199.6, 169.3, 157.1, 148.5 (2C), 142.8, 138.6, 137.6, 137.1, 134.8, 134.6, 132.0, 131.0, 130.3, 129.9, 129.8, 128.4, 127.7, 127.54, 127.51, 127.3, 126.2, 126.1, 125.9, 120.8, 82.4, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 29.0 (2C), 26.8, 22.2 (2C) ppm; HRMS (ES) m/z calcd. for $C_{31}H_{29}ClNO_3$ $[M + H]^+$: 498.1830; found 498.1836.

(*E*)-1-(3-(2-(7-Chloroquinolin-2-yl)vinyl)phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propan-1-one (9) via Base Mediated Transesterification of 13. Acetate **13** (8.5 g, 0.017 mol) was charged at room temperature into a mixture of THF (56.9 mL) and methanol (37.4 mL), taken in a dry 25 mL round-bottom flask equipped with a stir bar, condenser, and a nitrogen inlet. KOH (1.436 g, 0.025 mol) was added to the stirred suspension at room temperature under a flow of nitrogen. The reaction mixture was then allowed to stir at 45 °C for 6 h. During this interval, the initial yellow colored suspension gradually became a brown colored solution. Upon complete consumption of the starting material, as indicated by TLC, the reaction mixture was cooled to room temperature and treated with saturated Na_2SO_4 solution (40 mL). The organic layer was decanted off, and the solid residue was dissolved in 50 mL of water. The aqueous layer thus obtained was extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and then evaporated under vacuum to obtain a yellow semisolid. The crude residue thus obtained was purified by column chromatography using 30% EtOAc−hexanes to obtain **9** (6.2 g, 80% yield, 99% purity from HPLC analysis) as a pale yellow solid. mp 158−161 °C; IR (KBr) 3330 (br), 2972, 2927, 1685, 1596, 1497, 1431, 1406, 1559, 1294, 1162, 1152, 1132, 1076, 967, 949, 930, 888, 862, 841, 616, 536, and 471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 8.41 (d, J = 8.8 Hz, 1H), 8.34 (s, 1H), 8.08−7.85 (m, 6H), 7.68−7.48 (m, 3H), 7.38 (dd, J = 7.7, 1.3 Hz, 1H), 7.28 (dd, J = 7.4, 1.3 Hz, 1H), 7.18 (td, J = 7.4, 1.5 Hz, 1H), 7.13 (td, J = 7.5, 1.6 Hz, 1H), 5.02 (s, 1H), 3.47−3.39 (m, 1H), 3.32−3.26 (m, 1H), 1.55 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 18 °C) δ = 199.5, 156.6, 148.0, 146.8, 139.7, 137.3, 136.58, 136.57, 134.3, 134.1, 131.4, 131.4, 129.8, 129.4, 129.3, 128.0, 127.2, 127.0, 126.8, 126.5, 125.6, 125.4, 120.3, 72.0, 41.7, 31.8 (2C), 28.5 (2C) ppm; HRMS (ES) m/z calcd. for $C_{29}H_{27}ClNO_2$ $[M + H]^+$: 456.1730; found 456.1742. calcd for $C_{29}H_{26}NO_2Cl$: C 76.4%, H 5.8%, N 3.1%, Cl 7.8%; found: C 76.6%, H 5.9%, N 3.2%, Cl 7.9%.

Methyl 2-Iodobenzoate (11c). 2-Iodobenzoic acid (7 g, 0.0283 mol) was dissolved in methanol (70 mL) taken in a dry 250 mL

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round-bottom flask, equipped with a stir bar, condenser, and calcium chloride guard tube. The reaction mixture was stirred at room temperature in order to dissolve all solids and obtain a clear colorless solution. Concentrated H_2SO_4 (0.9 mL) was added dropwise into the reaction mixture at room temperature. The reaction mass was now allowed to reflux for 24 h, after which it was allowed to cool to room temperature. Methanol was then evaporated completely from the reaction mixture under vacuum, and the brown syrupy liquid obtained was neutralized carefully with saturated $NaHCO_3$ solution (20 mL). The product was extracted into hexanes (2 × 50 mL). The organic layers were combined and passed through a short silica gel plug, which was subsequently washed with ethyl acetate (100 mL). The eluted fractions, containing the product, were concentrated under vacuum to obtain **11c** (7 g, 94% yield, 99% purity from HPLC analysis) as a clear pale yellow liquid, which was pure enough to be employed directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 7.99 (dd, J = 7.9, 0.9 Hz, 1H), 7.80 (dd, J = 7.8, 1.6 Hz, 1H), 7.40 (td, J = 7.7, 1.1 Hz, 1H), 7.15 (td, J = 7.9, 1.8 Hz, 1H), 3.93 (s, 3H) ppm.

2-(2-Iodophenyl)propan-2-ol (10c). The title compound was prepared following a modification of a literature protocol.[24] Thus, magnesium turnings (1.17 g, 0.0488 mol) were taken in a dry 100 mL two-neck round-bottom flask, equipped with a stir bar, condenser, and an argon inlet. The reaction vessel was now evacuated, flame-dried under vacuum, and then allowed to cool under argon. Dry Et_2O (20 mL) was added into the reaction flask. A solution of methyl iodide (3.34 mL, 0.053 mol) in dry Et_2O (10 mL) was now introduced dropwise at room temperature over a period of 30 min. Thereafter, the reaction mixture was allowed to stir at room temperature for 1 h to ensure complete consumption of magnesium. The MeMgI solution, thus prepared, was now cooled to 0 °C. A solution of methyl 2-iodobenzoate **11c** (4 g, 0.0152 mol) in dry Et_2O (10 mL) was added dropwise into the cooled MeMgI solution over a period of 15 min. The reaction mixture obtained was allowed to warm to room temperature and then refluxed for 1 h when the initial green colored reaction mass turned into a brown colored suspension. The progress of the reaction was checked by TLC. Upon complete consumption of the starting material, the reaction mass was first cooled to 0 °C, and then added dropwise into a stirred mixture of saturated NH_4Cl solution (50 mL), ice, and diethyl ether (20 mL). After 30 min of stirring, the organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The organic layers were combined, dried over potassium carbonate, and evaporated under vacuum to obtain a brown colored syrup (3.26 g, containing about 89% **10c**) that was employed directly for the next step. The proportion of the required iodo-carbinol in the crude product mixture was determined by comparing its HPLC chromatogram with that of a sample, purified from the crude product mixture by column chromatography and subsequently characterized on the basis of ^{1}H NMR. The iodo-carbinol **10c** not only was sensitive to light but also decomposed gradually on a silica-gel column. ^{1}H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 7.96 (dd, J = 7.9, 1.3 Hz, 1H), 7.62 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (td, J = 8.1, 1.3 Hz, 1H), 6.90 (td, J = 7.8, 1.8 Hz, 1H), 1.76 (s, 6H) ppm.

Mizoroki–Heck Reaction between the Iodo-Carbinol 10c and Allyl Alcohol 3: (*E*)-1-(3-(2-(7-Chloroquinolin-2-yl)vinyl)-phenyl)-3-(2-(2-hydroxypropan-2-yl)phenyl)propan-1-one (9). Dimethylacetamide (14 mL), briefly sparged with nitrogen for 15 min, was taken in a 50 mL round-bottom flask, equipped with a stir bar, nitrogen inlet, and air condenser. The crude sample of **10c** (3.2 g, 89% purity from HPLC, 11 mmol) obtained in the previous step was charged into the reaction vessel at room temperature along with the allyl alcohol **3** (2.33 g, 7.2 mmol), $Pd(OAc)_2$ trimer (4.8 mg, 0.007 mmol), lithium acetate (1.48 g, 22.4 mol), tetrabutylammonium chloride (5.03 g, 1.8 mmol), and lithium chloride (377 mg, 8.9 mmol). The reaction mixture obtained was stirred at room temperature for 15 min and then at 120 °C for 1.5 days until complete consumption of the starting material was noted. The progress of the reaction was monitored by TLC and HPLC/LC-MS. HPLC/LC-MS analysis of the reaction mixture showed the following profile with time: (a) after 14 h: 32% **9**, 16% **3**; (b) after 24 h: 60% **9**, 6% **3**; (c) after 30 h: 81% **9**, 0% **3**. After completion of the reaction, the reaction mass was cooled to room temperature, diluted with 100 mL of ice-cold water, and then allowed to stir at room temperature for 15 min when a dark colored gummy material separated out. The aqueous layer was decanted off and extracted with dichloromethane (2 × 100 mL). The dichloromethane extracts were now used to dissolve the precipitated gummy material in the reaction vessel. The entire solution obtained was dried over anhydrous sodium sulfate and evaporated under vacuum to obtain a dark colored gummy mass. This was purified by column chromatography to obtain the Mizoroki–Heck reaction product **9** as a pale yellow solid (2.5 g, 73%, 94% purity from HPLC analysis).

Small-Scale Preparation of (2-(2-(3-(3(*S*)-(2-(7-Chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol) (6) Using Enzymatic Reduction. To a solution of D-glucose (202 mg), KRED-NADH-129 (13.5 mg, 150U), GDH-102 (0.7 mg, 100U) and NAD^+ (3.2 mg) in 50 mM phosphate buffer pH 7.0 (9.5 mL), 0.5 mL of a 100 mg/mL solution of the ketone **9** in DMSO was added, and the ensuing mixture was stirred at 25 °C, while maintaining the pH at 7.0 with 1 M NaOH. Samples were prepared for assay by diluting a 25 mL aliquot of the reaction to 1 mL with MeCN and drying ($MgSO_4$). The liquid was decanted off and analyzed by SFC (*vide infra*). When the reaction had stopped, the mixture was extracted with EtOAc (2 × 10 mL). Emulsions were removed from the organic layer by filtration through Celite. The organic layer was then washed with sat. brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the product as a colorless oil (30 mg). This was determined to be 60:40 **9**:**6** by both NMR and SFC. The ee of the alcohol was determined as >99% by SFC.

Small-Scale Preparation of (2-(2-(3-(3(*S*)-(2-(7-Chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol) (6) Using Biotage Endeavor. A vessel of a Biotage Endeavor catalyst screening system was charged with the ketone **9** (880 mg, 1.92 mmol). The vessel was purged with nitrogen (5 × 10 bar); then, deoxygenated isopropyl alcohol (2.4 mL) was added. A solution of [((*R*)-Xyl-BINAP)((*R*)-DAIPEN)$RuCl_2$] (2.23 mg, 0.0018 mmol) in deoxygenated isopropanol (2.37 mL) was prepared, and a 1.0 mL (0.00076 mmol) aliquot of this solution was added to the vessel. A solution of potassium *tert*-butoxide (1.0 M in THF, 0.93 mL) in deoxygenated isopropyl alcohol (8 mL) was prepared. A 1.0 mL aliquot of this solution was charged to the vessel; then, the vessel was pressurized to 0.8 bar with hydrogen. The vessel was heated to 40 °C and then pressurized to 8 bar with hydrogen and stirred for 18 h at 8 bar hydrogen pressure and 40 °C while monitoring hydrogen uptake, which showed completion to have occurred after 2 h. The temperature was allowed to fall to room temperature, the pressure was released, and then a solution of acetic acid (0.2 mL, approximately 0.19 mmol of a solution of 265 μL, 4.62 mmol in isopropanol (4.5 mL)) was added. The solvent was evaporated to give (*S*)-**6** (96.9%ee) as a brown, viscous oil (conversion by ^{1}H NMR, 100%).

(2-(2-(3-(3(*S*)-(2-(7-Chloro-2-quinolinyl)ethenyl)phenyl)-3-hydroxypropyl)phenyl)-2-propanol) (6).[2,18,21,25] A 600 mL pressure vessel was charged with the ketone **9** (20.0 g, 43.9 mmol) and isopropanol (100 mL). The vessel was purged with nitrogen (5 × 7 bar); then, solutions of [((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)$RuCl_2$] (9.8 mg, 0.0088 mmol) in deoxygenated isopropanol (1 mL) and potassium *tert*-butoxide (1.0 M in THF, 3.51 mL) were added. The vessel was pressurized to 7.6 bar with hydrogen and then heated to 40 °C while stirring. Initially, the pressure rose to 8.0 bar. After 3.5 h, uptake stopped at 5.9 bar. The reaction was stirred for a further 30 min and then cooled to 30 °C, the pressure was released, and acetic acid (251 μL, 4.39 mmol) was added. A small sample was withdrawn and analyzed showing the enantiomeric excess of the crude **6** to be 98.8% (*S*). About 70 mL of solvent was removed using a rotary evaporator. Toluene (50 mL) and 10% sodium carbonate solution (25 mL) were added, the mixture was shaken, and the layers were separated. The aqueous phase was extracted with toluene (50 mL), the combined organic phases were dried (Na_2SO_4) and filtered, and about 60 mL of solvent was removed using a rotary evaporator. The solution was seeded with a small quantity of **6** and stirred for 30 min; then, heptane (50 mL) was added over 4 h. The suspension was stirred for 18 h and

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then filtered, and the solid was washed with heptane−toluene (1:2, 4 × 20 mL) to give (*S*)-**6** as a white, granular solid (17.3 g, 86%, 99.6%ee (*S*)). Evaporation of the liquors gave a brown foam (2.41 g). Analysis showed the product **6** present in this fraction to have an enantiomeric excess of 87.2% (*S*). mp 119−120 °C; $[\alpha]_D^{25}$ −23.2° (*c* = 1.0, THF). Sample from known route using (−)-DIP-Cl[1,11,12] (99.8% ee) −24.4° (*c* = 1.0, THF); IR (KBr) 3366, 1507, 1595, 1497, 1442, 1407, 1310, 1160, 1144, 1066, 966, 926, 670, 831, 759, and 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 18 °C) δ = 8.08 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.71 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.43 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.38−7.30 (m, 4H), 7.26 (td, *J* = 7.2, 1.6 Hz, 1H), 7.22 (td, *J* = 7.3, 1.4 Hz, 1H), 7.14 (td, *J* = 7.4, 2.0 Hz, 1H), 4.74−4.70 (m, 1H), 3.3 (br s, 1 H), 3.28−3.20 (m, 2H), 3.16−3.10 (m, 1H), 2.5 (br s, 1H), 2.17−2.10 (m, 2H), 1.70 (s, 3H) and 1.67 (s, 3H) ppm. ^1H NMR (400 MHz, C_6D_6, 18 °C) δ = 8.46 (d, 1H, *J* = 1.6 Hz),8.01 (d, 1H, *J* = 16.4 Hz), 7.79 (s, 1H), 7.53−7.46 (m, 3H), 7.38 (d, 1H, *J* = 7.6 Hz), 7.33 (d, 1H, *J* = 8.0 Hz), 7.30−7.13 (m, 7H), 4.75−4.71 (m, 1H), 3.46−3.38 (m, 1H), 3.26−3.20 (m, 1H), 3.03 (br s, 1H), 2.25−2.19 (m), 2.03 (br s, 1H), 1.54 (s, 3H) and 1.53 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 18 °C) δ = 156.9, 148.5, 145.4, 145.0, 140.2, 136.2, 136.1, 135.5, 135.2, 131.4, 128.8, 128.6, 128.4, 128.1, 127.2, 127.0, 126.4, 126.3, 126.0, 125.6, 125.5, 124.7, 119.5, 74.1, 72.9, 41.9, 32.1, 32.0, and 29.6 ppm; ^{13}C NMR (100 MHz, C_6D_6, 18 °C) δ = 157.2. 149.2, 146.4, 145.8, 140.7, 136.8, 135.9, 135.7, 135.6, 131.8, 129.0, 128.9, 128.7, 128.6, 127.9, 127.9, 127.5, 126.9, 126.9, 126.4, 126.0, 125.8, 120.1, 125.5, 74.0, 73.0, 42.6, 32.2, 32.1, and 30.1 ppm. *m*/*z* ES 460 ($[M^{37}Cl + H]^+$, 40), 458 ($[M^{35}Cl + H]^+$, 100).

■ ASSOCIATED CONTENT

Supporting Information

.

Method of chiral analysis for **6**, and NMR spectra of **6**, **9**, **10b**, **10c**, **11b**, **11c**, **12**, and **13**. Reaction conditions employed in unsuccessful reactions between **3** and **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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