JOC The Journal of Organic Chemistry

FEATURED ARTICLE

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Catalytic Asymmetric Synthesis of a Tertiary Benzylic Carbon Center via Phenol-Directed Alkene Hydrogenation

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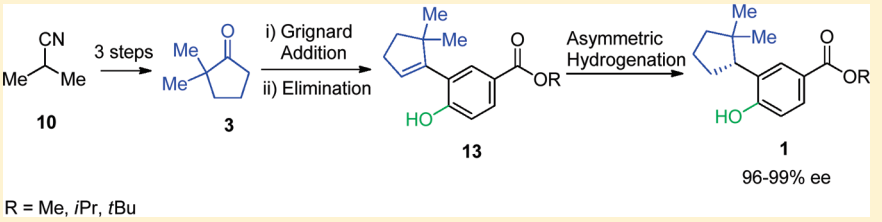
Supporting Information

ABSTRACT:



An expeditious synthetic approach to chiral phenol **1**, a key building block in the preparation of a series of drug candidates, is reported. The strategy includes a cost-effective and readily scalable route to cyclopentanone **3** from isobutyronitrile (**10**). The sterically hindered and enolizable ketone **3** was subsequently employed in a challenging Grignard addition mediated by $LaCl_3 \cdot 2LiCl$. A novel preparation of the lanthanide reagent required for this transformation is described. To complete the process, a highly enantioselective hydrogenation step afforded the target (**1**). The importance of the phenol group to the success of this asymmetric transformation is discussed.

INTRODUCTION

The preparation of chiral benzylic stereocenters represents a significant challenge in organic synthesis. Several methods affording these structural motifs make use of functional handles which must subsequently be removed if they are not part of the target molecules (asymmetric conjugate addition to enones, asymmetric arylation of ketones).[1] During the course of a recent development program, chiral phenol **1** emerged as a key building block in the synthesis of a series of drug candidates (Figure 1). Asymmetric hydrogenation of an alkene precursor would constitute an attractive method to generate this type of chiral compound without the use of a carbonyl-containing functional handle. Such a method[2] could also be applied to the preparation of tolterodine[3] (**2**, Detrol LA), a structurally related commercial drug employed in the treatment of urinary bladder disorders. The development of a short and practical synthesis of **1**, including an asymmetric hydrogenation step, became a primary focus of our group.

The original synthesis of **1** employed by the Discovery Chemistry team is depicted in Scheme 1. Boronate ester **6** was prepared in two steps from 2,2-dimethylcyclopentanone (**3**) by generation of vinyl triflate **4** and subsequent Pd-catalyzed coupling with bis(pinacolato)diboron (**5**) (37% overall yield). Bromide **8** was obtained from the commercially available carboxylic acid **7** by esterification and protection of the phenol group as a tetrahydro-2*H*-pyran-2-yl (THP) ether. Suzuki−Miyaura coupling of **6** and **8** produced alkene **9** (80%). Solvolysis of the THP ether group of **9** was followed by

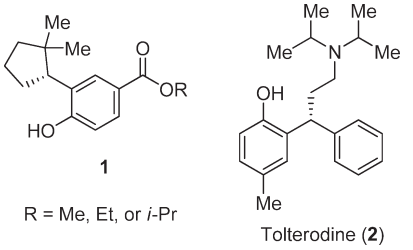
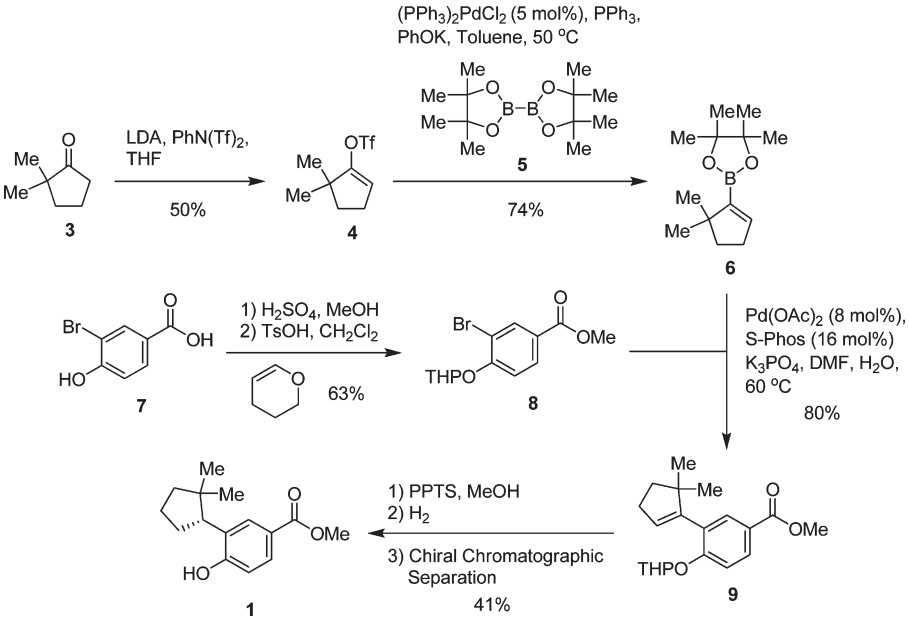


Figure 1. Chiral intermediate **1** and tolterodine.

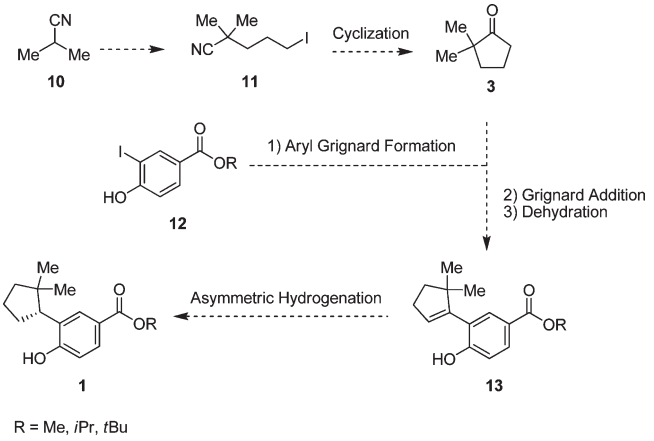
hydrogenation of the alkene and the resulting racemic mixture was separated by chiral chromatography to provide phenol **1**. This approach to **1** comprised several features that made it unsuitable for large-scale application. First, cyclopentanone **3** is an expensive starting material with limited availability.[4] Consequently, any route that employs **3** should involve a minimum number of linear steps from **3** to **1**. The linear sequence from **3** to **1** in the drug discovery sequence is rather long (six steps), and the overall yield is low (12%). Additionally, the use of protecting groups is not desirable for long-term application. Finally, the benzylic stereogenic center should be generated enantioselectively to improve the overall yield and avoid chiral separation of a racemic mixture.

Received: May 9, 2011
Published: June 01, 2011

Scheme 1. Discovery Synthesis of Chiral Phenol 1



Scheme 2. Proposed Approach to Chiral Phenol 1



Our proposed alternative approach to phenol **1** is shown in Scheme 2. Cyclopentanone **3** has been synthesized previously via an intramolecular anionic cyclization process initiated by formation of an alkyl Grignard reagent from iodide **11**.[5,6] However, low yields (<10%) of **3** were obtained in our hands using this Grignard reagent and it was desired to improve on these results by employing an alkyl lithium reagent as an alternative. An addition−elimination sequence would constitute an attractive method to obtain **13** from **3**. This addition would ideally be performed by preparing an aryl Grignard reagent directly from unprotected phenol **12**.[7] The addition employing sterically hindered cyclopentanone **3** was expected to be challenging due to competing ketone enolization.[8] Lanthanide salts have been utilized in the literature to improve the yields of such transformations.[9] The development of an enantioselective hydrogenation of the alkene group of **13** would complete our synthesis of **1**. A lot of attention has recently been focused on the asymmetric hydrogenation of unfunctionalized alkenes employing iridium complexes and the BARF counterion.[10] However, the use of this counterion on manufacturing scale is prohibited by cost,[11] unless very low catalyst loadings (below 0.05 mol %) can be achieved. On the other hand, it was conceived that the phenol group could serve as a complexing agent in the asymmetric hydrogenation, thus allowing the transformation to proceed with high enantioselectivity employing rhodium catalysis as is the case in the well documented rhodium catalyzed asymmetric hydrogenation of enamides.[12]

RESULTS AND DISCUSSION

2,2-Dimethylcyclopentanone (**3**) was prepared via a simple, three-step reaction sequence using inexpensive and readily available starting materials and reagents (Scheme 3). Isobutyronitrile (**10**) was deprotonated using LDA, and the resulting lithium anion was alkylated with 1-bromo-3-chloropropane. Byproduct **15** was obtained along with the desired adduct **14**. The amounts of **15** generated were observed to be dependent on the temperature of the reaction, lower temperatures allowing for a more selective transformation. Upon performing the transformation at −70 °C, the products (**14**/**15**) were obtained in a >100/1 ratio; however, this ratio was 4.2/1 when the reaction was conducted at −40 °C. Chloride **14** was isolated after aqueous workup/distillation and converted to iodide **11** via a Finkelstein reaction (NaI, acetone, reflux). The product (**11**), purified by distillation, was prepared in 83% yield from starting material **10**.

A solution of iodide **11** was added to *n*-hexyllithium in THF at −5 °C to afford, after acidification using aqueous oxalic acid, 2,2-dimethylcyclopentanone (**3**) in 81% yield (99% assay yield). The addition of a THF solution of **11** to *n*-hexyllithium gave a higher yield (99% assay yield) than the inverse mode of addition (adding *n*-hexyllithium to a solution of **11**, 83% assay yield). Two equivalents of *n*-hexyllithium were utilized in this transformation to maximize the yield of **3** since the equivalent of iodohexane generated from lithium-halogen exchange immediately reacted

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Scheme 3. Preparation of 2,2-Dimethylcyclopentanone (3)

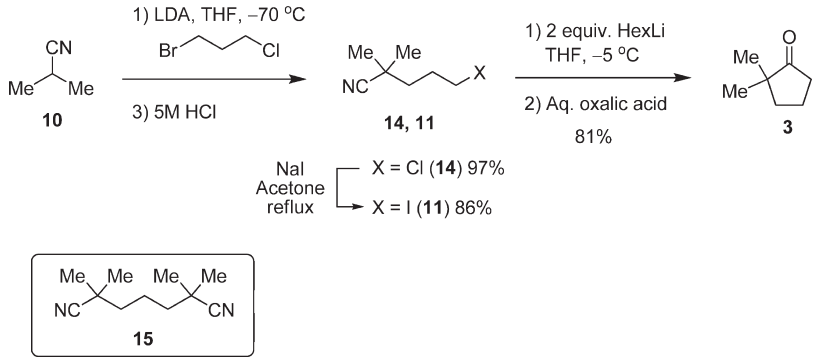
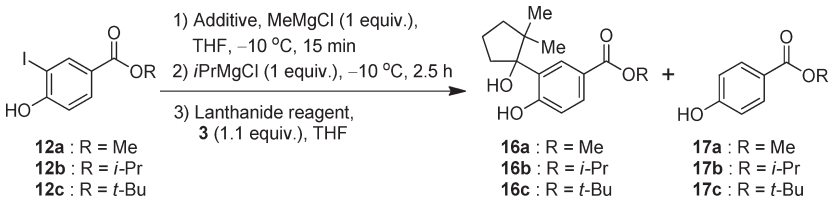


Table 1. Grignard Addition To Generate Tertiary Alcohol 16[a]



entry	substrate	R	additive (*x* equiv)	lanthanide reagent (*x* equiv)	*T* (°C)	time (h)	**16** (%)	**17** (%)
1	**12a**	Me	LiCl (1)	none	−20	12	0	83
2	**12a**	Me	LiCl (1)	$CeCl_3$ "rods" (1.3)	−20	12	18	39
3	**12a**	Me	LiCl (1)	$CeCl_3 \cdot 2LiCl$ (1.3)	−20	12	0	52
4	**12a**	Me	LiCl (1)	$CeCl_3 \cdot 2LiCl$ (1.3)	−20	12	27	27
5	**12a**	Me	LiCl (1)	$LaCl_3 \cdot 2LiCl$ (1.3)	−20	12	34	28
6	**12a**	Me	LiCl (1)	$LaCl_3 \cdot 2LiCl$ (1.3)	−20	1.5	39	29
7	**12a**	Me	LiO*i*Pr (1)	$LaCl_3 \cdot 2LiCl$ (1.3)	−20	1.5	44	26
8	**12b**	*i*-Pr	none	$LaCl_3 \cdot 2LiCl$ (1.3)	−10	1.5	17	57
9	**12b**	*i*-Pr	LiO*i*Pr(1)	$LaCl_3 \cdot 2LiCl$ (1.3)	−10	1.5	50	30
10	**12c**	*t*-Bu	LiO*i*Pr(1)	$LaCl_3 \cdot 2LiCl$ (1.3)	23	1.5	71	23
11	**12c**	*t*-Bu	LiO*i*Pr(1)	$LaCl_3 \cdot 2LiCl$ (0.5)	23	1.5	46	35

[a] Reaction conditions: 18 mL of solvent per gram of **12** utilized. Assay yields determined by HPLC versus an authentic standard are reported except for **16** in entries 9 and 10.

with a second equivalent of alkyllithium reagent to afford dodecane. The ketone **3** (bp 145 °C) was separated from dodecane (bp 216 °C) via distillation.[13,14]

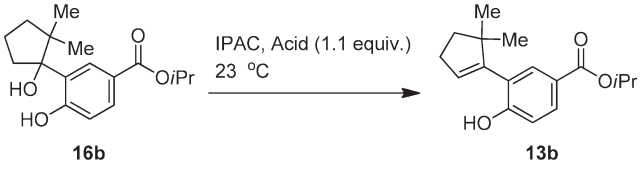
With an efficient route to 2,2-dimethylcyclopentanone (**3**) in hand, work focused on conversion of **3** to alkene **13**. An aryl Grignard reagent was generated from iodide **12a** (R = Me) according to the procedure reported by Knochel and co-workers.[7] In this protocol, 1 equivalent of MeMgCl was employed to deprotonate the phenol group of **12a** and 1 equivalent of *i*-PrMgCl was subsequently added to effect the desired Mg−I exchange. The transformation was carried out at −30 °C in the presence of 1 equivalent of LiCl. We found that for substrate **12a** (R = Me), aging of the reaction mixture at −10 °C for 2.5 h after addition of all the reagents was necessary to observe complete conversion of the starting iodide. To the resulting aryl Grignard reagent was added a solution of **3** in THF and the reaction mixture was aged at −20 °C for 12 h. No desired alcohol **16a** was formed in this experiment and the only product of the reaction was phenol **17a** (83%, entry 1).[15] This result was consistent with the known propensity of cyclic ketones, particularly sterically hindered α-substituted ketones, to undergo enolization rather than carbonyl addition reactions. To help address this problem, the use of rod-shaped $CeCl_3$ THF−solvate crystals has been reported by Conlon and co-workers.[16] Thus a suspension of $CeCl_3$ THF−solvate "rods" was generated according to the reported procedure and ketone **3** was added to the mixture at 23 °C. The suspension was agitated for 1 h and subsequently added to a solution of the Grignard reagent prepared from **12a** (R = Me). The resulting mixture was aged at −20 °C for 12 h to afford **16a** in a disappointing 18% assay yield (entry 2).

An alternative method to prepare lanthanum chloride reagents was reported by Knochel and co-workers.[9c] This procedure involves the use of solutions of $CeCl_3 \cdot 2LiCl$ or $LaCl_3 \cdot 2LiCl$ in THF to improve the yield of desired carbonyl addition

dx.doi.org/10.1021/jo200941r |*J. Org. Chem.* 2011, 76, 5198–5206

products. However, several features of the procedure described to prepare these solutions were unattractive for application on large scale including: (i) extended heat cycles up to 160 °C, (ii) drying of nonstirrable $CeCl_3 \cdot 2LiCl$ or $LaCl_3 \cdot 2LiCl$ solid complexes, (iii) low and variable concentrations of the final lanthanide solutions, (iv) time-consuming operations and the need for multireactor processing to prepare the desired solutions. As a result, we elected to prepare these reagents in a simplified manner that should be suitable for larger scale application. We used anhydrous $LaCl_3$ or $CeCl_3$ to prepare 0.125 M solutions of $CeCl_3 \cdot 2LiCl$ or $LaCl_3 \cdot 2LiCl$ in THF by adding commercially available solutions of LiCl (0.5 M in THF) to the lanthanide salt and heating the resulting mixtures at reflux for 12 h. Undissolved materials remained at the end of that heating period in the case of $CeCl_3$ and thus a filtration step was required to obtain a clear solution.[17] However, using $LaCl_3$, a homogeneous solution was conveniently obtained at the end of the heating period. After the initial 0.125 M solutions were obtained, distillation of most of the THF was performed to produce solutions of $CeCl_3 \cdot 2LiCl$ or $LaCl_3 \cdot 2LiCl$ with a concentration range of 0.7 M to 1.0 M.[18] Ketone **3** was added at 23 °C to a solution of $CeCl_3 \cdot 2LiCl$ thus prepared, and the resulting mixture was aged for 1 h. This solution was added to a cold (−20 °C) solution of the Grignard reagent generated from iodide **12a**, and the mixture was agitated for 12 h to afford alcohol **16a** in 27% yield (Table 1, entry 4). The same experiment performed with $LaCl_3 \cdot 2LiCl$ instead of $CeCl_3 \cdot 2LiCl$ afforded **16a** in 34% yield (entry 5). One should note that the order of addition is critical to the success of this transformation. Interestingly, when the order of addition was changed and a $CeCl_3 \cdot 2LiCl$ solution was added to the aryl Grignard reagent, followed by addition of ketone **3**, no desired product **16a** was observed (entry 3). Owing to the ease of preparation of the $LaCl_3 \cdot 2LiCl$ reagent (no filtration step), we elected to pursue the optimization of the Grignard addition using this reagent rather than $CeCl_3 \cdot 2LiCl$. The reaction time after addition of $LaCl_3 \cdot 2LiCl$ and **3** was shortened to 1.5 h, and LiCl was replaced with LiO*i*Pr as an additive during Grignard formation. As a result, the yield of **16a** was increased from 34% to 44% (entry 5 vs entry 7).

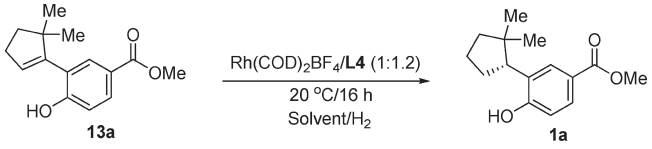
Table 2. Elimination To Generate Alkene 13b[a]



entry	acid	time (h)	yield (%)
1	methanesulfonic acid	1.5	90[b]
2	HCl	3.0	91
3	H_2SO_4	1.0	89[b]

[a] Reaction conditions: 4.7 mL of solvent per gram of **16b** utilized. [b] Assay yields determined by HPLC versus an authentic standard are reported.

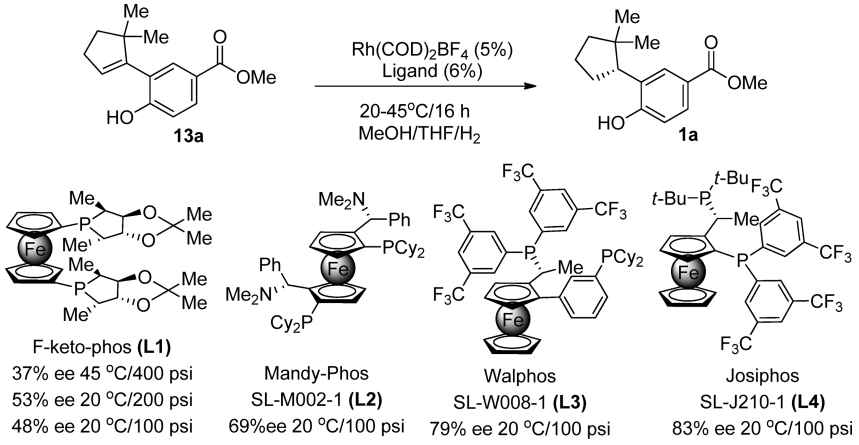
Table 3. Reaction Screen for Asymmetric Hydrogenation of 13a Using Josiphos SL-J-210-1 as Ligand[a]



entry	solvent	pressure (psi)	Rh loading (%)	additive[b]	conversion (%)	ee (%)
1	MeOH	200	5		95	79
2	THF	200	5		100	94
3	EtOAc	200	5		99	77
4	Toluene	200	5		98	96
5	THF	200	1	NaCl	75	95
6	THF	200	1	Et_3N	100	97
7	THF	50	1	Et_3N	90	95
8	THF	50	0.5	Et_3N	40	
9	THF	200	0.1	Et_3N	100	97
10	THF	200	0.1	Et_3N	100	99[c]

[a] Reaction Conditions: **13a** (100 mg), catalyst/ligand added as stock solution, 10 vol of THF. [b] 5 mol % of additive was used. [c] 97.7 g scale, 3 vol of THF.

Scheme 4. High-Throughput Screening Results for Asymmetric Hydrogenation of 13a[a]



[a] The enantiomer of **1a** was obtained as major isomer using ligands **L1** and **L3**.

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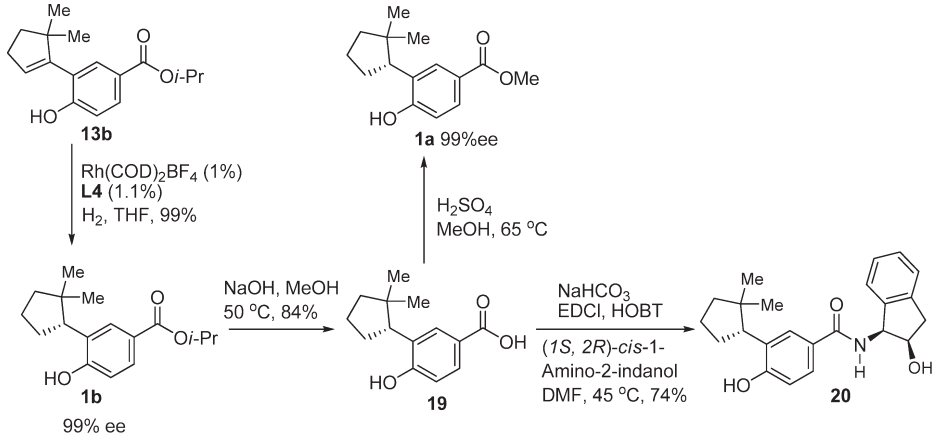
Scheme 5. Absolute Stereochemistry Determination for Phenols 1a and 1b



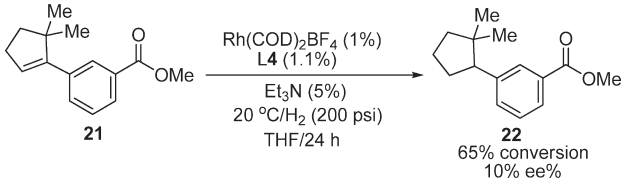
However, it was noted that the combined yields of products **16a** and **17a** obtained utilizing methyl ester **12a** and either $LaCl_3 \cdot 2$ LiCl or $CeCl_3 \cdot 2$LiCl in the Grignard addition ranged from 54% to 70% (entries 4−7). The remaining mass balance was attributed to the formation of a number of other byproducts, as indicated by HPLC analysis of the reaction mixtures. Some of these byproducts corresponded to the methyl ester function of **12a** reacting under these conditions (byproduct masses were correlated by LCMS). Consequently, the same transformation with bulkier ester derivatives was studied in order to suppress nucleophilic addition to the ester group. The Grignard addition with corresponding isopropyl ester (substrate **12b**) was conducted with LiO*i*Pr as additive and $LaCl_3 \cdot 2$LiCl as lanthanide source and tertiary alcohol **16b** was generated in 50% yield (entry 9). It is worth noting that the same experiment performed in the absence of LiO*i*Pr provided **16b** in significantly reduced yield (17%, entry 8). Using *tert*-butyl ester **12c** as starting material, the Grignard addition could be conducted at 22 °C[19] and **16c** was isolated in 71% yield (entry 10). The transformation could be carried out with substoichiometric amounts of $LaCl_3 \cdot 2$LiCl, though the yield of **16c** obtained in this instance was considerably reduced (46%, entry 11 vs 71%, entry 10). The combined yields of products **16** and **17** generated using isopropyl ester **12b** or *tert*-butyl ester **12c** in this transformation were 80% to 94% (entries 8−11). These joint recoveries constitute a marked improvement relative to those achieved utilizing methyl ester **12a** for the same reaction.

The elimination to generate asymmetric hydrogenation precursor **13b** proceeded uneventfully employing various acid sources as described in Table 2. The reaction conditions described in entry 2 (Table 2) were utilized to perform the same transformation starting with methyl ester **16a** to afford **13a** (87% yield).

A large collection of ligands (72) was evaluated for the rhodium-catalyzed asymmetric hydrogenation of alkene **13a** using $Rh(COD)_2BF_4$ as catalyst. Four of the ligands provided >85% conversion and >50% ee (Scheme 4), with Josiphos SL-J-210-1 providing the highest enantiomeric excess (83%).

The transformation was further explored with regard to solvents, pressure, additives, and rhodium loadings employing Josiphos SL-J-210-1 as ligand (Table 3). The choice of solvent proved to have a significant impact on the enantioselectivity of the hydrogenation. Relatively low enantiomeric excesses were obtained with MeOH (79% ee, entry 1) and EtOAc (77% ee, entry 3), whereas

Scheme 6. Asymmetric Hydrogenation of a Substrate Lacking the Phenol Moiety (21)



higher enantiomeric excesses were observed using THF (94% ee, entry 2) and toluene (96% ee, entry 4). It is well established that trace amounts of impurities may inhibit Rh-catalyzed hydrogenations by attenuating the activity of the catalyst.[20] Accordingly, the transformation failed to go to completion in the presence of small amounts of NaCl (entry 5). In the presence of Et_3N (5 mol %), the catalyst loading could be reduced from 5 mol % (entry 2) to 0.1% (entry 9) and the hydrogenation ee increased from 94% to 97%. The optimized reaction conditions (0.1% Rh loading, 200 psi, 5 mol % Et_3N, THF, entry 9) were used in an experiment performed starting with 98 g of **13a** (entry 10). The transformation proceeded in 1 h at 22 °C (98.7% ee). The crude reaction mixture was filtered through silica gel, concentrated, triturated in EtOAc/heptane, and filtered. Using this protocol, phenol **1a** was obtained as a crystalline white solid in 96% corrected yield and 99.5% ee (upgraded during trituration).

The hydrogenation conditions developed for **13a** were applied to the corresponding isopropyl ester (**13b**) and phenol **1b** was obtained in 99% corrected yield and 99% ee (Scheme 5). The absolute stereochemistry of the stereogenic center in **1a** and **1b** was determined via single-crystal X-ray crystallographic analysis of amide **20**. This compound was synthesized by hydrolysis of **1b** under basic conditions (NaOH, MeOH, 50 °C, 84%) followed by coupling of the resulting carboxylic acid (**19**) with commercially available (1*S*,2*R*)-*cis*-1-amino-2-indanol (EDCI, HOBT, $NaHCO_3$, DMF, 45 °C, 74%). A crystal of **20** suitable for the X-ray diffraction study was provided by recrystallization of the material in EtOAc/hexane. Acid **19** was converted to **1a** via Fisher esterification. The enantiomer of **1a** generated via this sequence of reactions was the same as that obtained by asymmetric hydrogenation of **13a**. Consequently, the absolute

dx.doi.org/10.1021/jo200941r |*J. Org. Chem.* 2011, 76, 5198–5206

configuration of the product obtained in this transformation was shown to be independent of the nature of the ester function of the starting material.

It is worth noting that the presence of the hydroxyl group in **13a** and **13b** was essential for the success of the asymmetric hydrogenation. For example, when the transformation was performed with a substrate lacking the phenol moiety (**21**) and under the same experimental conditions, it failed to reach completion after 24 h and the product was obtained in only 10% ee (Scheme 6).[21]

CONCLUSION

In summary, a rapid access to chiral phenol **1**, a key building block in the preparation of a series of drugs candidates, was developed. The strategy includes six chemical steps, and the target molecule was prepared in 31% overall yield from isobutyronitrile (**10**). The sequence of reactions features a challenging Grignard addition conducted in the presence of $LaCl_3 \cdot 2LiCl$ (50% yield using **12b** as substrate, 70% yield using **12c** as substrate) as well as a highly enantioselective hydrogenation of an aryl substituted alkene (99% yield, 99% ee). A novel preparation of the lanthanide reagent used for the Grignard addition was developed. The importance of the phenol group to the success of this asymmetric transformation was discussed.

EXPERIMENTAL SECTION

5-Chloro-2,2-dimethylpentanenitrile (14). To a solution of *i*-Pr_2NH (101.8 mL, 0.72 mol) in THF (680 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes, 288 mL, 0.72 mol). The mixture was cooled to −65 °C, and isobutyronitrile (**10**, 50.0 g, 0.72 mol) was added as a liquid over the course of 10 min. The reaction mixture was warmed to −20 °C over a period of 45 min and cooled to −78 °C. The resulting slurry was added (via cannula) over the course of 3 h to an agitated solution of 1-bromo-3-chloropropane (113.9 g, 0.72 mol) in THF (300 mL) at −78 °C (internal temperature was maintained below −68 °C). The original vessel was rinsed using THF (200 mL), and the rinse solution was added to the reaction mixture (via cannula). The mixture was agitated for 10 min at −70 °C, and DI water (220 mL) was added. Aqueous HCl (5 M, 215 mL) was added over a period of 10 min while the internal temperature was maintained below 0 °C. MTBE (250 mL) was added, the mixture was agitated vigorously, and the layers were separated. The aqueous phase was extracted with MTBE (100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (250 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by distillation (80 to 100 mmHg, head temperature 175 to 200 °C) afforded **14** as an oil (101.0 g, 96.8% corrected yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 6 H), 1.67−1.72 (m, 2 H), 1.94−2.01 (m, 2 H), 3.59 (t, J = 6.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 28.4, 32.0, 38.4, 44.5, 124.6; HRMS (ESI) calcd for $C_7H_{12}N$ 110.0970, found 110.0959.

5-Iodo-2,2-dimethylpentanenitrile (11). To a solution of **14** (35.4 g, 0.24 mol) in acetone (250 mL) was added NaI (79.8 g, 0.53 mol). The mixture was warmed to reflux, agitated for 18 h, and cooled to 22 °C. The suspension was filtered, and the filtrate was concentrated under reduced pressure. MTBE (100 mL) was added, and the slurry was filtered. The filtrate was washed twice with saturated aqueous $Na_2S_2O_3$ (2 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by distillation (1 mmHg, head temperature 62 to 66 °C) afforded **11** as an oil (49.8 g, 86.2% corrected yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 6 H), 1.63−1.67 (m, 2 H), 1.98−2.05 (m, 2 H), 3.22 (t, J = 6.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.3, 26.6, 29.1, 31.7, 41.8, 124.6; HRMS (ESI) calcd for $C_7H_{12}NI$ 237.0014, found 237.0005.

2,2-Dimethylcyclopentanone (3). To a cold (−20 °C) solution of *n*-hexylithium (2.3 M in hexanes, 74.6 mL, 0.18 mol, 2.0 equiv) in THF (40 mL) was added a solution of **11** (21.0 g, 0.9 mol) in THF (89 mL) over a period of 20 min (the internal temperature was maintained below −5 °C). The reaction mixture was agitated at −5 °C for 1 h, and 1.6 M aqueous oxalic acid (112 mL, 0.18 mol, 2.0 equiv) was added over the course of 15 min while the temperature was maintained below 20 °C. The mixture was agitated at 20 °C for 1 h. MTBE (110 mL) and DI water (110 mL) were added to the reaction mixture. The layers were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by distillation using a Snyder column (300 mmHg, head temperature 110−112 °C) afforded **3** as an oil (11.92 g, 81% corrected yield, 32.4 wt % dodecane in isolated oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 6 H), 1.80 (t, J = 6.5 Hz, 2 H), 1.50 (quintet, J = 7.4 Hz, 2 H), 2.26 (t, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 23.7, 37.1, 38.5, 44.9, 123.8; HRMS (ESI) calcd for $C_7H_{12}O$ 112.0888, found 112.0887.

***tert*-Butyl 4-Hydroxy-3-iodobenzoate (12c).** To a solution of 4-hydroxy-3-iodobenzoic acid (2.5 g, 9.47 mmol) and DMAP (0.06 g, 0.47 mmol) in *tert*-butyl alcohol (60 mL) was added a solution of DCC (2.15 g, 10.4 mmol) in THF (20 mL) over a period of 30 min at 22 °C. The reaction mixture was agitated for 12 h and concentrated under reduced pressure. Diethyl ether (200 mL) and oxalic acid (2.0 g, 27.0 mmol) were added, and the mixture was filtered through a short silica pad. The filtrate was washed with saturated aqueous $NaHCO_3$, water, and brine. The solution was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (15 g silica gel, 20% EtOAc/hexanes) of the residual material yielded 2.7 g (89%) of **12c** as a solid: mp 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9 H), 6.13 (s, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 8.30 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 81.5, 84.9, 114.5, 126.2, 131.8, 140.1, 158.5, 164.3; HRMS (ESI) calcd for $C_{11}H_{12}IO_3$ 318.9831, found 318.9824.

$LaCl_3 \cdot 2LiCl$ Solution. To a commercial solution of LiCl (0.5 M in THF, 300 mL) were added dry THF (300 mL) and anhydrous $LaCl_3$ (18.4 g, 0.075 mol) under nitrogen. The suspension was warmed to reflux and agitated for 12 h (a solution was obtained). The majority of the THF was distilled (approximately 510 mL) at 760 mmHg. Dry THF (100 mL) was added, the distillation was continued (another 100 mL of THF was distilled), and the solution was cooled to 20 °C. The measured $LaCl_3$ concentration of the solution (volume ∼100 mL) was 0.808 M (ICP-MS). The measured water content of the solution was 350 ppm (KF). The reagent was stored under nitrogen prior to use.

Methyl 4-Hydroxy-3-(1-hydroxy-2,2-dimethylcyclopentyl)-benzoate (16a, Entry 7, Table 1). To a cold (−25 °C) solution of methyl 4-hydroxy-3-iodobenzoate (**12a**, 5.0 g, 18.0 mmol) in THF (30 mL) was added a solution of LiO*i*Pr (2.0 M in THF, 9.9 mL, 19.8 mmol) over a period of 10 min, and the reaction mixture was agitated for 15 min. MeMgCl (2.5 M in THF, 7.9 mL, 19.8 mmol) was added over the course of 30 min (the internal temperature was maintained below −17 °C), and the mixture was agitated at −25 °C for 30 min. *i*-PrMgCl (2.0 M in THF, 9.9 mL, 19.8 mmol) was added over a period of 10 min. The reaction mixture was agitated for 2 h and cooled to −32 °C.

In a separate flask, 2,2-dimethylcyclopentanone (**3**, 2.5 mL, 19.8 mmol) was added to a solution of $LaCl_3 \cdot 2LiCl$ (0.71 M in THF, 32.9 mL, 23.4 mmol) at 22 °C. The mixture was agitated for 1 h and cooled to −10 °C. The $LaCl_3 \cdot 2LiCl$ solution was added to the Grignard solution via cannula over a period of 1 h (the internal temperature was maintained below −20 °C). The reaction mixture was agitated for 1.5 h at −20 °C (44% assay yield). Aqueous citric acid (1 M, 25 mL) was added over the course of 30 min, and the reaction mixture was warmed

to 22 °C. IPAc (300 mL) and aqueous HCl (1 M, 10 mL) were added and the layers were separated. The aqueous layer was extracted with IPAc (200 mL). The combined organic extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (35 g silica gel, 0−15% MTBE/heptane) of the residual material was followed by trituration of the chromatographed product in MTBE (5 mL) and heptane (100 mL) to yield **16a** as a white solid (1.54 g, 32% yield): mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.09 (s, 3 H), 1.59−1.61 (m, 1 H), 1.87−1.94 (m, 4 H), 2.79−2.82 (m, 1 H), 3.21 (s, 1 H), 3.83 (s, 3 H), 6.80 (d, J = 8.0 Hz, 1 H), 7.71 (s, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 10.19 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 22.3, 25.9, 38.3, 38.6, 47.4, 51.9, 90.4, 117.5, 120.2, 124.9, 130.0, 130.8, 161.8, 167.5; HRMS (ESI) calcd for $C_{15}H_{21}O_4$ 265.1440, found 265.1422.

Isopropyl 4-Hydroxy-3-(1-hydroxy-2,2-dimethylcyclopentyl)-benzoate (16b, Entry 9, Table 1). To a cold (−5 °C) solution of isopropyl 4-hydroxy-3-iodobenzoate (**12b**, 4.0 g, 13.0 mmol) in THF (25 mL) was added a solution of LiO*i*Pr (2.0 M in THF, 7.9 mL, 15.7 mmol) over a period of 10 min, and the reaction mixture was agitated for 15 min. MeMgCl (2.5 M in THF, 6.3 mL, 15.7 mmol) was added over the course of 30 min (the internal temperature was maintained below 0 °C), and the mixture was agitated at −5 °C for 30 min. *i*-PrMgCl (2.0 M in THF, 9.5 mL, 15.7 mmol) was added over a period of 10 min. The reaction mixture was agitated for 2 h and cooled to −20 °C.

In a separate flask, 2,2-dimethylcyclopentanone (**3**, 2.0 mL, 15.7 mmol) was added to a solution of $LaCl_3 \cdot 2LiCl$ (0.71 M in THF, 23.9 mL, 17.0 mmol) at 22 °C. The mixture was agitated for 1 h and cooled to −10 °C. The $LaCl_3 \cdot 2LiCl$ solution was added to the Grignard solution via cannula over a period of 1 h (the internal temperature was maintained below −10 °C). The reaction mixture was agitated for 1.5 h at −10 °C. Aqueous citric acid (1 M, 20 mL) was added over the course of 30 min, and the reaction mixture was warmed to 22 °C. IPAc (300 mL) and aqueous HCl (1 M, 10 mL) were added, and the layers were separated. The aqueous layer was extracted with IPAc (200 mL). The combined organic extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (30 g silica gel, 0−15% MTBE/heptane) of the residual material was followed by trituration of the chromatographed product in MTBE (5 mL) and heptane (100 mL) to yield **16b** as a white solid (1.90 g, 50% yield): mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (s, 3 H), 1.11 (s, 3 H), 1.34 (d, J = 8.0 Hz, 6 H), 1.59−1.65 (m, 1H), 1.88−1.92 (m, 4H), 2.42 (s, 1H), 2.83−2.90 (m, 1 H), 5.14−5.24 (m, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 7.77 (s, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 9.96 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 22.0, 22.3, 25.9, 38.3, 38.8, 47.4, 68.1, 90.6, 117.4, 121.1, 124.8, 130.0, 130.6, 161.3, 166.4; HRMS (ESI) calcd for $C_{17}H_{25}O_4$ 293.1753, found 293.1733.

***tert*-Butyl 4-Hydroxy-3-(1-hydroxy-2,2-dimethylcyclopentyl)-benzoate (16c, Entry 10, Table 1).** To a cold (0 °C) solution of *tert*-butyl 4-hydroxy-3-iodobenzoate (**12c**, 3.0 g, 9.4 mmol) in THF (20 mL) was added a solution of LiO*i*Pr (2.0 M in THF, 5.2 mL, 10.3 mmol) over a period of 10 min, and the reaction mixture was agitated for 15 min. MeMgCl (2.5 M in THF, 4.1 mL, 10.3 mmol) was added over the course of 30 min (the internal temperature was maintained below 5 °C), and the mixture was agitated at 0 °C for 30 min. *i*-PrMgCl (2.0 M in THF, 9.5 mL, 15.7 mmol) was added over a period of 10 min. The reaction mixture was warmed to 22 °C, agitated for 2 h, and cooled to 0 °C.

In a separate flask, 2,2-dimethylcyclopentanone (**3**, 1.3 mL, 10.3 mmol) was added to a solution of $LaCl_3 \cdot 2LiCl$ (0.78 M in THF, 15.7 mL, 12.2 mmol) at 22 °C. The mixture was agitated for 1 h. The $LaCl_3 \cdot 2LiCl$ solution was added to the Grignard solution via cannula over a period of 10 min. The reaction mixture was warmed to 22 °C and agitated for 1.5 h. Aqueous citric acid (1 M, 20 mL) was added over the course of 30 min. IPAc (300 mL) and aqueous HCl (1 M, 30 mL) were added and the layers were separated. The aqueous layer was extracted with IPAc (200 mL). The combined organic extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (25 g silica gel, 0−15% MTBE/heptane) of the residual material afforded **16c** as a white solid (2.04 g, 71% yield): mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (s, 3 H), 1.10 (s, 3 H), 1.56 (s, 9 H), 1.61−1.64 (m, 1 H), 1.86−1.94 (m, 4 H), 2.80−2.86 (m, 2 H), 6.81 (d, J = 8.0 Hz, 1 H), 7.73−7.77 (m, 2 H), 10.04 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 22.4, 25.9, 28.3, 38.3, 38.9, 47.4, 80.6, 90.7, 117.3, 122.3, 124.7, 129.8, 130.6, 161.4, 166.1; HRMS (ESI) calcd for $C_{18}H_{26}O_4Na$ 329.1723, found 329.1721.

Isopropyl 3-(5,5-Dimethylcyclopent-1-enyl)-4-hydroxybenzoate (13b, Entry 2, Table 2). To a solution of **16b** (2.8 g, 9.4 mmol) in IPAC (10 mL) at 22 °C was added HCl (5 M in IPA, 2.8 mL, 14.1 mmol). The reaction mixture was agitated for 1.5 h, and IPAC (200 mL) was added. The mixture was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (25 g silica gel, 20% MTBE/heptane) of the residual material afforded **13b** as a colorless oil (2.3 g, 91% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 1.35 (d, J = 8.0 Hz, 6 H), 1.92 (t, J = 8.0 H, 2 H), 2.49 (dt, J = 8.0 and 2.4 Hz, 2 H), 5.18−5.26 (m, 1 H), 5.79 (t, J = 2.4 Hz, 1 H), 6.01 (s, 1H), 6.93−6.99 (m, 1 H), 7.76−7.80 (m, 1 H), 7.85−7.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 27.2, 30.1, 40.6, 48.3, 67.9, 114.7, 122.5, 123.5, 130.4, 130.9, 131.6, 146.9, 157.3, 166.0; HRMS (ESI) calcd for $C_{17}H_{23}O_3$ 275.1647, found 275.1630.

Methyl 3-(5,5-Dimethylcyclopent-1-enyl)-4-hydroxybenzoate (13a). The procedure reported to prepare **13b** (entry 2, Table 2) was utilized. **16a** (1.50 g, 5.7 mmol) replaced **16b** as starting material, and **13a** was isolated as white solid (1.22 g, 87% yield): mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 6 H), 1.93 (t, J = 8.0 H, 2 H), 2.50 (dt, J = 8.0 and 2.4 Hz, 2 H), 3.88 (s, 3 H), 5.80 (t, J = 2.4 Hz, 1 H), 5.89 (s, 1H), 6.95−6.99 (m, 1 H), 7.76−7.80 (m, 1 H), 7.86−7.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 30.0, 40.5, 48.2, 51.8, 114.7, 121.5, 123.5, 130.5, 130.9, 131.5, 146.7, 157.5, 166.9; HRMS (ESI) calcd for $C_{15}H_{19}O_3$ 247.1334, found 247.1339.

(*R*)-Methyl 3-(2,2-Dimethylcyclopentyl)-4-hydroxybenzoate (1a, Entry 10, Table 3). A solution of **13a** (99.7 g, 0.41 mol), $Rh(COD)_2BF_4$ (165 mg, 0.41 mmol), and Josiphos SL-J-210-1 (**L4**) (364 mg, 0.44 mmol) in THF (300 mL) was charged to a Parr reactor. The reactor was purged with argon once and with H_2 three times (200 psig). The contents of the reactor were agitated at 20 °C for 30 min under an atmosphere of H_2 (200 psig). The solution was purged with N_2, filtered through silica gel (20 g), and concentrated under reduced pressure. The residue was triturated (5% EtOAc/heptane, 120 mL) and filtered to afford **1a** as a solid (95.0 g, 96% yield, 99.5% ee): chiral SFC analysis, OD-H column, 250 mm × 4.6 mm, 5 μm; MeOH, 252 nm, *S* enantiomer at 3.07 min, *R* enantiomer (**1a**) at 3.38 min; mp 127−129 °C; $[\alpha]_D^{23}$ +47.5 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (s, 3H), 1.04 (s, 3H), 1.38−2.21 (m, 6H), 3.12−3.26 (m, 1H), 3.89 (s, 3H), 6.08 (s, 1H), 6.83 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 8.3, 1.4 Hz, 1H), 7.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 23.5, 29.0, 30.5, 41.6, 43.0, 47.2, 52.0, 115.2, 121.7, 128.7, 129.0, 131.2, 159.0, 167.8; HRMS (ESI) calcd for $C_{15}H_{21}O_3$ 249.1491, found 249.1467.

(*R*)-Isopropyl 3-(2,2-Dimethylcyclopentyl)-4-hydroxybenzoate (1b). The procedure reported to prepare **1a** was utilized. **13b** (1.00 g, 3.6 mmol) replaced **13a** as starting material, and **1b** was isolated as white solid (0.99 g, 99% yield, 99% ee): chiral HPLC analysis: OD-H column, 250 mm × 4.6 mm, 5 μm; 1.5 mL/min; 5 μL; 25 °C; 3% IPA/*n*-hexane, isocratic; 254 nm, *S* enantiomer at 7.40 min, *R* enantiomer (**1b**) at 7.88 min; mp 135−137 °C; $[\alpha]_D^{23}$ +55.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (s, 3H), 1.04 (s, 3H), 1.35 (dd, J = 6.2, 1.4 Hz, 6H), 1.52−1.68 (m, 2H), 1.68−1.91 (m, 2H), 1.92−2.17 (m, 2H), 3.17

(dd, J = 8.0, 10.1 Hz, 1H), 5.22 (septet, J = 6.2 Hz, 1H), 5.83 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 2.1, 8.4 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 23.5, 29.0, 30.5, 41.6, 43.0, 47.3, 68.1, 115.0, 122.6, 128.5, 128.8, 131.1, 158.3, 166.66; HRMS (ESI) calcd for $C_{17}H_{25}O_3$ 277.1804, found 277.1822.

3-[(*R*)-2,2-Dimethylcyclopentyl]-4-hydroxy-*N*-[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]benzamide (20). To a solution of **1b** (0.5 g, 1.8 mmol) in MeOH (5 mL) was added aqueous NaOH (5 M, 3.7 mL, 18.1 mmol). The reaction mixture was warmed to 60 °C, agitated for 16 h, and cooled to 22 °C. Water (20 mL) and aqueous HCl (5 M, 4 mL, 20 mL) were added (final pH = 1), and the mixture was extracted with MTBE (2 × 75 mL). The combined organic extracts were washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure.

The residue (crude **19**) was dissolved in DMF (5 mL) at 22 °C. $NaHCO_3$ (0.7 g, 8.1 mmol), (1*S*,2*R*)-*cis*-1-amino-2-indanol (0.4 g, 2.7 mmol), EDCI (0.51 g, 2.7 mmol), and HOBt (0.13 g, 0.27 mmol) were added to the solution. The mixture was warmed to 50 °C, agitated for 16 h, and cooled to 22 °C. EtOAc (100 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$, aqueous HCl (5 M, 50 mL), water (50 mL), and brine. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (10 g silica gel, 10−50% EtOAc/hexanes) of the residual material afforded crude **20** as an oil. The oil was dissolved in EtOAc (5 mL), and hexanes was added at 22 °C over the course of 45 min. The suspension was filtered, and the cake was dried on frit to afford **20** as a white solid (0.47 g, 62% yield): mp 204−206 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 0.74 (s, 3 H), 0.87−0.93 (m, 1 H), 1.06 (s, 3 H), 1.26−1.36 (m, 1 H), 1.57−1.68 (m, 2 H), 1.72−2.03 (m, 3 H), 2.09−2.20 (m, 1 H), 3.00 (d, J = 16.0 Hz, 1 H), 3.21 (dd, J = 20 and 8.0 Hz, 1 H), 3.39−3.42 (m, 1 H), 4.66 (t, J = 4 Hz, 1 H), 5.56 (d, J = 8.0 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 7.23−7.30 (m, 4 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.80 (d, J = 4.0 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 23.2, 24.3, 29.6, 31.5, 41.0, 42.7, 43.9, 47.8, 59.1, 74.3, 115.6, 125.4, 125.5, 126.2, 127.2, 128.0, 129.0, 129.9, 130.7, 141.8, 142.6, 160.7, 170.6; HRMS (ESI) calcd for $C_{23}H_{28}NO_3$ 366.2069, found 366. 2062.

Methyl 3-(5,5-Dimethylcyclopent-1-enyl)benzoate (21). To a solution of *i*-Pr_2NH (4.58 mL, 32.7 mmol) in THF (40 mL) at −78 °C was added *n*-BuLi (13.1 mL, 32.7 mmol, 2.5 M in Hexanes) over a period of 10 min. 2,2-Dimethylcyclopentanone (**3**, 3.5 g, 31.2 mmol) was added over a period of 15 min, and the solution was agitated at −78 °C for 30 min. *N*-Phenylbis(trifluoromethanesulfonimide) (11.1 g, 31.2 mmol) was added, and the reaction mixture was warmed to 20 °C over a period of 3 h. The mixture was concentrated under reduced pressure, and MTBE (100 mL) was added. The suspension was filtered, and the filtrate was concentrated under reduced pressure. Chromatographic purification (40 g silica gel, 2% EtOAc/hexanes) of the residual material afforded **4** (3.8 g, 50% yield) as a colorless oil.

Vinyl trifluoromethanesulfonate **4** (1.2 g, 5 mmol) was dissolved in dioxane (10 mL) and water (10 mL) at 20 °C. 3-(Methoxycarbonyl)-phenylboronic acid (1.1 g, 6 mmol), K_3PO_4 (3.0 g, 15.0 mmol), and $PdCl_2[(p\text{-}Me_2NPh)P\text{-}t\text{-}Bu_2]_2$ (71 mg, 0.1 mmol) were added, and the suspension was degassed using argon. The reaction mixture was warmed to 80 °C, agitated for 30 min, and cooled to 20 °C. MTBE was added (30 mL), and the phases were separated. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Chromatographic purification (silica gel, 0−10% EtOAc/hexanes) of the residual material afforded **21** (0.8 g, 89% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.87 (t, J = 7.0 Hz, 2H), 2.38 (td, J = 2.4, 7.0 Hz, 2H), 3.90 (s, 3H), 5.79 (t, J = 2.4 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.51 (t, J = 9.5 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.96−8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 28.8, 41.6, 46.0, 51.4, 127.0, 127.3, 127.8, 128.0, 129.2, 131.2, 137.6, 150.5, 166.5; HRMS (ESI) calcd for $C_{15}H_{19}O_2$ 231.1385, found 231.1382.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra as well as the CIF for compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We wish to dedicate this manuscript to the career and legacy of Professor Edward Piers (1938−2010, University of British Columbia). We thank Jack Hu, Kevin Turney, and Jenny Chen for analytical support. We thank Richard Staples for performing the single-crystal X-ray analysis included.

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(2) Application of the method described in this manuscript to the asymmetric synthesis of tolterodine has been reported by our group: Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13* (7), 1881–1883.

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(4) Price of **3** from Sigma-Aldrich: ~$2.5/g on 5 g scale. We experienced difficulties sourcing **3** as several suppliers failed to deliver the requested material because of the use of inadequate synthetic routes (>20 g scale).

(5) Synthesis of **11**: Larcheveque, M.; Debal, A.; Cuvigny, T. *Bull. Soc. Chim. Fr.* **1974**, 1710–1714.

(6) Synthesis of **3** from **11**: Larcheveque, M.; Debal, A.; Cuvigny, T. *J. Organomet. Chem.* **1975**, *87*, 25–31.

(7) The preparation of the ethyl ester variant of **12** has been reported: Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288–2289.

(8) The rate of deprotonation of cyclopentanones by basic reagents has been shown to be higher than that associated with the deprotonation of cyclohexanones or acyclic ketones: Shechter, H.; Collis, M. J.; Dessy, R.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2905–2910 Consequently, this undesired reaction pathway is particularly problematic in the case of addition of basic nucleophiles to cyclopentanones..

(9) Reported yields improve drastically for addition of Grignards reagents to cyclopentanone derivatives if the transformations are performed in the presence of lanthanide salts. For examples, see: (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398. (b) Dimitrov, V.; Bratovanov, S.; Simona, S.; Kostova, K. *Tet. Lett.* **1994**, *35*, 6713–6716. (c) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497–500.

(10) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–2899.

(11) The cost of the Na salt of BARF is $100/g on a 100 g scale (SynQuest Fluorochemicals).

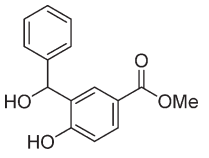
(12) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143.

(13) Under nonoptimized distillation conditions, dodecane was only partially separated from **3** and the isolated material contained 32.4 wt%

of dodecane. High purity **3** (>96 wt%) from Aldrich was utilized to screen the lanthanide-catalyzed Grignard addition reaction.

(14) Although *n*-butyllithium was also a suitable mediator, the byproduct octane (bp 126 °C) could not be readily separated from **3**.

(15) When benzaldehyde was added to the Grignard reagent instead of ketone **3**, alcohol **18** was isolated in 72% yield.



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(16) Conlon, D. A.; Kumbe, D.; Moeder, C.; Hardiman, M.; Hutson, G.; Sailer, L. *Adv. Synth. Catal.* **2004**, *346*, 1307–1315.

(17) Due to the necessity to filter these solids, the stoichiometry of Ce relative to that of Li in the final lanthanide solution cannot be assessed with certainty.

(18) Concentrations of La and Ce were measured by ICP-MS.

(19) The Grignard addition performed at 23 °C with substrates **12a** and **12b** produced complex mixtures of products.

(20) Limanto, J.; Shultz, C. S.; Dorner, B.; Desmond, R. A.; Devine, P. N.; Krska, S. W. *J. Org. Chem.* **2008**, *73*, 1639–1642.

(21) A complete substrate scope for this transformation has been reported separately: Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13* (7), 1881–1883.