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A Concise Synthesis of Racemic 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol for a Potent $C_{17,20}$-Lyase Inhibitor

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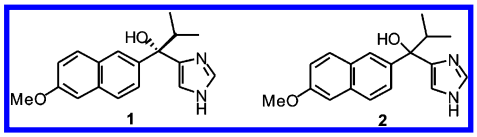
Abstract:

The development of a practical and scaleable synthesis of 1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (2) is described. Racemate 2 was synthesized from commercially available 4(5)-imidazolecarboxyaldehyde (7) in three steps excluding chromatography. 4(5)-Cyanoimidazole (10) was prepared from 7 in good yield in a one-pot reaction. A Grignard reaction of cyanoimidazole 10 with isopropylmagnesium bromide followed by the addition of aqueous sulfuric acid formed acylimidazole 9. The final racemate 2 was obtained by the direct Grignard reaction of acylimidazole 9 without N-protection. This process was accomplished efficiently to produce 2 in 70% overall yield from 7 in a large-scale synthesis.

Introduction

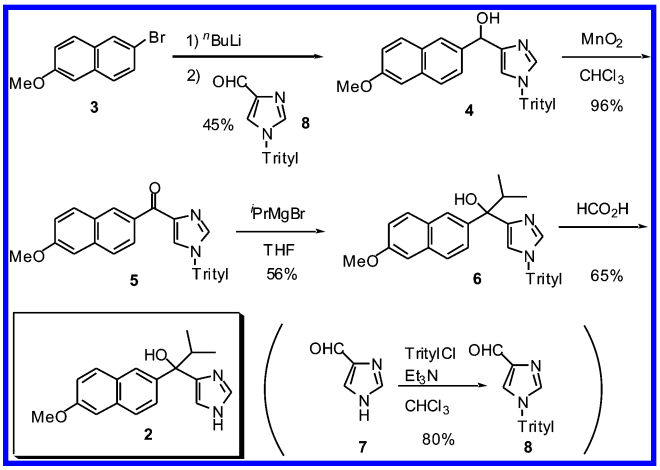
$C_{17,20}$-Lyase, which is a key enzyme involved in androgen biosynthesis, is thought to be a promising target for the treatment of androgen-dependent prostate cancer.[1] In fact, $C_{17,20}$-lyase inhibitors have been reported, and some of them have entered clinical trials.[2] In previous papers, Matsunaga, Tasaka, and co-workers have identified (1*S*)-1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (**1**) as a novel inhibitor of $C_{17,20}$-lyase.[3] Therefore, we sought a large-scale synthesis suitable for the preparation of racemate **2** of a potent $C_{17,20}$-lyase inhibitor **1**. In this paper, we describe a practical and scaleable three-step chromatography-free synthesis of **2**.



Results and Discussion

The synthesis route of **2** was reported by Matsunaga, Tasaka, and co-workers.[3a] As shown in Scheme 1, 1-trityl-1*H*-imidazole-4-carboxyaldehyde (**8**) was prepared from 4(5)-imidazolecarboxyaldehyde (**7**) by reaction with tritylchloride.[4] The reaction of **3** with the aldehyde **8** was carried out via lithiation to give the secondary alcohol **4**. **4** was oxidized with manganese dioxide to provide the corresponding ketone **5**. The addition of isopropylmagnesium bromide to **5** to provide the tertiary alcohol **6** followed by removal of the trityl group furnished the desired compound **2**.

Scheme 1. **Initial synthesis of 2**



Although **2** is able to be prepared using this route, there are some problems for further scale-up. For instance, (i) **2** and **4** were produced in low yield by chromatographic purification; (ii) $CHCl_3$, which is highly toxic, was used as a solvent for N-protection of **7** and the oxidation of **4**; (iii) large amounts of manganese dioxide were used in the oxidation of **4**. Therefore, to avoid these drawbacks we have developed an alternative practical process for the synthesis of **2**.

Retrosynthetic analysis revealed that the most efficient route toward the synthesis of **2** would employ the late-stage coupling of the acylimidazole **9** and naphthalene fragment **3** (Scheme 2). Recently, we have discovered a convenient synthesis of 4(5)-alkylacyl-1*H*-imidazoles from commercially available 4(5)-imidazolecarboxyaldehyde (**7**) without an N-protecting group.[5] By using this synthesis, acylimidazole **9** could be derived simply from **7** via an intermediate nitrile **10**.

Cyanoimidazole **10** was prepared from **7** in a one-pot reaction (Scheme 3). A solution of **7** and hydroxylamine

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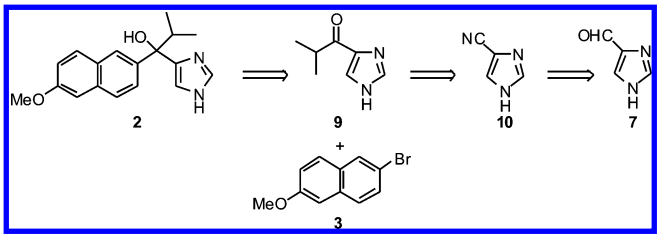
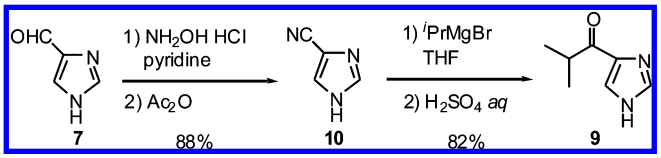
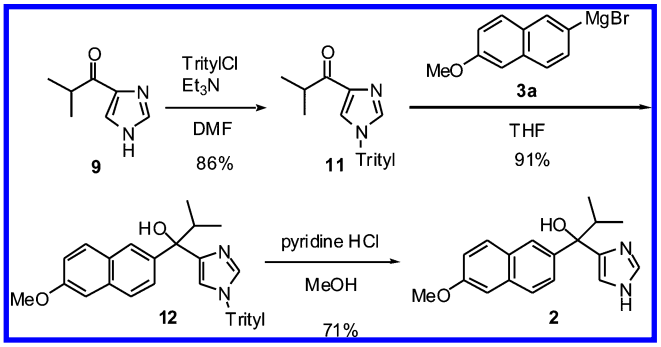
Scheme 2. **Retrosynthetic analysis**



Scheme 3. **Synthesis of 1-[1*H*-imidazol-4(5)-yl]-2-methylpropan-1-one (9)**



Scheme 4. **Synthesis of 2 from 9 with N-protection of the imidazole ring**



hydrochloride in pyridine was stirred at room temperature for 2 h, then treated with acetic anhydride, and stirred again at 110 °C for 2 h.[6] After the usual workup and recrystallization, cyanoimidazole **10** was obtained in 88% yield. Grignard reaction of **10** with isopropylmagnesium bromide (3 equiv) at room temperature for 3 h, followed by hydrolysis with sulfuric acid, gave 1-[1*H*-imidazol-4(5)-yl]-2-methylpropan-1-one (**9**) in 82% yield.

The reaction of **9** with tritylchloride/Et_3N in DMF proceeded smoothly to give the product **11** in good yield (86%) (Scheme 4). Next, to form the compound **12** from **11**, we carried out the Grignard reaction of **11** with **3a**. Grignard reagent **3a** was prepared from **3** and magnesium in THF at 20−25 °C. Addition of **3a** to **11** in THF at 0 °C, followed by stirring at room temperature for 5 h, formed the corresponding product **12** in high yield (91%). Finally, the N-deprotection of **12** using pyridinium hydrochloride in MeOH at 20−25 °C[7] successfully provided the desired product **2** as a crystalline solid in 71% yield.

In general, reactions of 4-acylimidazoles with Grignard reagents have used N-protecting groups on the imidazole ring.[8] On the other hand, it has been reported by some that the alkylation of non-protected 4(5)-formylimidazoles,[9] 4(5)-cyanoimidazoles,[5,10] 4(5)-imidazolecarboxylate,[10a,11] or 4(5)-acylimidazoles[10a] with excess Grignard reagents takes place to provide the corresponding products. We thought that the

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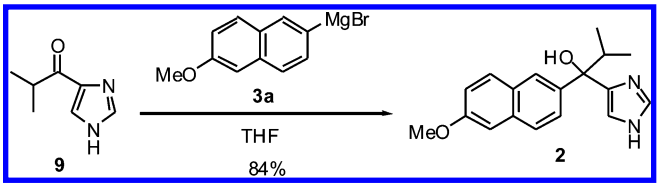
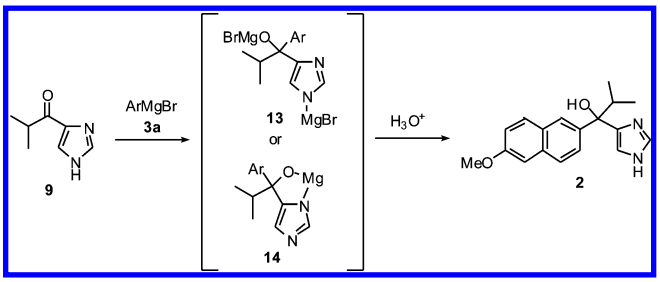
Scheme 5. **Synthesis of 2 from 9 without N-protection of the imidazole ring**



Scheme 6. **Proposed reaction mechanism of Grignard reaction of 9**



Grignard addition to compound **9** could be accomplished, without N-protection, to form **2** in one step. Accordingly, it was found that the desired compound **2** could be synthesized in 84% yield by using 2.8 equiv of Grignard reagent **3a**[12] (Scheme 5).

Although elucidation of the precise mechanism requires further detailed investigation, this reaction may be assumed to proceed via an intermediate **13** or **14**, as shown in Scheme 6. In consequence, this protecting free synthetic process was able to give **2** in three steps from commercially available 4(5)-imidazolecarboxyaldehyde (**7**) in 60% overall yield. Furthermore, the use of the crude intermediates **10** and **9** without purification via crystallization at each step, led to an increase of the overall yield of **2** from the starting material **7** (overall yield; 70%, Scheme 7). In fact, this process could produce **2** from **7** in a large-scale preparation.

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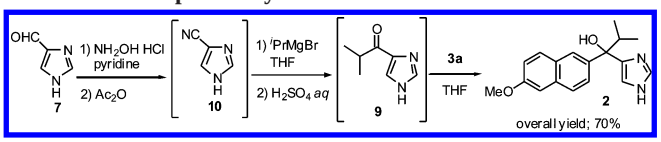
(12) In the case of using less than 2.8 equiv of Grignard reagent **3a**, the yield was decreased.

Scheme 7. **Improved synthesis of 2**



Conclusions

In summary, we have developed a convenient process for the practical large-scale synthesis of racemate **2** required for preparation of the potent enantiomer $C_{17,20}$-lyase inhibitor **1**. The desired compound **2** could be produced from commercially available 4(5)-imidazolecarboxyaldehyde (**7**) in three steps not only without chromatography but also without the requirement for N-protection of the imidazole ring.

Experimental Section

General Comments. ^{1}H NMR spectra were recorded on BRUKER-DPX 300 (300 MHz) and spectrometers using $CDCl_3$, DMSO-d_6 as the solvent with Me_4Si as the internal standard. ^{13}C NMR spectra were taken on BRUKER-DPX 300 (75 MHz) spectrometers using $CDCl_3$ as the solvent. Chemical shifts in ^{13}C NMR were measured relative to $CDCl_3$ and converted to the $\delta(Me_4Si)$ value using $\delta(CDCl_3) = 77.0$. IR spectra were determined on a HORIBA FT-210 spectrometer. MS was obtained on JEOL JMS-700T in Takada Analytical Research Laboratories, Ltd. Elemental analyses were also performed there. All materials were obtained from commercial supplies.

Synthetic Procedure for 4(5)-Cyanoimidazole (10). To a solution of 4(5)-imidazolecarboxyaldehyde (**7**) (50 g, 0.52 mol) in pyridine (150 mL) was added hydroxylamine hydrochloride (40.5 g, 0.585 mol). After stirring the mixture for 2 h at room temperature, the solution was heated to 80 °C, and acetic anhydride (92.3 mL, 0.978 mol) was added dropwise at 80−110 °C. The mixture was further stirred until the temperature reached room temperature, and was titrated to pH 7.9 with 30% aqueous sodium hydroxide solution. Ethyl acetate (380 mL) was added for extraction, and the aqueous layer was extracted again with ethyl acetate (250 mL). The organic layer was combined, washed with brine (×2), and concentrated under reduced pressure. Toluene (100 mL) was added to the residue, and the mixture was concentrated under reduced pressure (twice). The crystals formed were collected by filtration and washed with isopropyl ether (100 mL). The crystals were dried in vacuo (40 °C) to give 4(5)-cyanoimidazole (**10**)[13] (42.7 g, yield 88%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.91 (s, 1 H), 8.10 (s, 1 H); MS (EI): $m/z = 93$ ($M^{\bullet+}$), 66 ($M^{\bullet+} - HCN$).

Synthetic Procedure for 1-(1*H*-Imidazol-4(5)-yl)-2-methylpropan-1-one (9). A solution of 4(5)-cyanoimidazole (**10**) (42.7 g, 0.458 mol) in THF (500 mL) was added dropwise over 30 min to a solution (1.4 L, 1.47 mol) of 1.1 M isopropylmagnesium bromide in THF below 10 °C under a nitrogen atmosphere.[13] The mixture was stirred at room temperature for 3 h. Water (430 mL) and 10% aqueous sulfuric acid solution (860 mL) were added dropwise, and the mixture was stirred at 30 min and titrated to pH 8 with 30% aqueous sodium hydroxide solution. After the organic layer was separated, the aqueous layer was extracted with ethyl acetate (300 mL × 2). The organic layers were combined, and the mixture was washed with aqueous sodium hydrogen carbonate and brine and concentrated under reduced pressure. The crystals formed were collected by filtration and washed with isopropyl ether (300 mL). The crystals were dried in vacuo (40 °C) to give 1-(1*H*-imidazol-4(5)-yl)-2-methylpropan-1-one (**9**)[5] (51.9 g, yield 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, $J = 6.9$ Hz, 6 H), 3.31−3.41 (m, 1 H), 7.81 (s, 1 H), 7.87 (s, 1 H), 11.39 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 138.5, 135.9, 127.9, 36.7, 19.2; IR (KBr): $\nu = 1664$ (CO) cm^{-1}; MS (EI): $m/z = 138$ (M^+); Anal. calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.83; H, 7.44; N, 20.21.

Synthetic Procedure for 2-Methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-one (11). To a solution of 1-(1*H*-imidazol-4(5)-yl)-2-methylpropan-1-one (**9**) (8.6 g, 62.2 mmol) in DMF (10 mL) was added dropwise triethylamine (12.1 mL, 86.8 mmol). Tritylchloride (20.8 g, 74.5 mmol) was added to the mixture. After stirring the mixture for 2.5 h at room temperature, triethylamine (1 mL) and tritylchloride (2 g) were added to the mixture. The mixture was further stirred for 2 h at room temperature and added to water. The crystals formed were collected by filtration and washed with water. The crystals were added to ethyl acetate (50 mL). After stirring the mixture for 1 h at room temperature, the crystals were collected by filtration and washed with ethyl acetate (10 mL). The crystals were dried in vacuo (40 °C) to give 2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-one (**11**) (20.3 g, yield 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, $J = 6.9$ Hz, 6 H), 3.59−3.73 (m, 1 H), 7.10−7.13 (m, 6 H), 7.34−7.36 (m, 9 H), 7.44 (d, $J = 1.1$ Hz, 1 H), 7.58 (d, $J = 1.2$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 141.8, 140.1, 139.1, 129.7, 128.4, 128.3, 125.8, 76.1, 35.8, 18.7; IR (KBr): $\nu = 1670$ (CO) cm^{-1}; MS (ESI): $m/z = 381$ (MH^+); Anal. calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 81.86; H, 6.44; N, 7.20.

Synthetic Procedure for 1-(6-Methoxy-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (12). THF (13 mL) was added to magnesium (1.7 g, 69.9 mmol) under a nitrogen atmosphere. Iodine (33 mg) was added, and the mixture was stirred. While keeping the mixture at less than 50 °C, a solution of 2-bromo-6-methoxynaphthalene (15.4 g, 65.0 mmol) in THF (39 mL) was added dropwise, and the mixture was stirred at 15−25 °C for 1 h. To a solution of 2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-one (**11**) (10.0 g, 26.3 mmol) in THF (100 mL) was added dropwise 1 M (6-methoxy-2-naphthyl)magnesium bromide (**3a**) in THF (42.0 mL, 42.0 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. Saturated aqueous sodium hydrogen carbonate (100 mL) and water (25 mL) were successively added dropwise. After the layers partitioned, the aqueous layer was extracted with ethyl acetate. The organic layers were combined, and the mixture was washed with brine and concentrated under reduced pressure. The

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concentration residue was broken up with ethyl acetate (40 mL), and the crystals were collected by filtration and washed with ethyl acetate (10 mL × 2). The crystals were dried in vacuo (40 °C) to give 1-(6-methoxy-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (**12**)[3a] (12.9 g, yield 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 2.46−2.59 (m, 1 H), 3.66 (s, 1 H), 3.90 (s, 3 H), 6.79 (d, J = 1.2 Hz, 1 H), 7.09−7.14 (m, 8 H), 7.31−7.34 (m, 10 H), 7.53 (dd, J = 8.6 and 1.7 Hz, 1 H), 7.62−7.70 (m, 2 H), 7.92 (s, 1 H).

Synthetic Procedure for 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (2) from 12. To a solution of 1-(6-methoxy-2-naphthyl)-2-methyl-1-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (**12**) (1.0 g, 1.86 mmol) in MeOH (5 mL) was added pyridinium hydrochloride (0.43 g, 3.72 mmol). The mixture was stirred at 50−60 °C for 5 h and titrated to pH 2 with 1 N aqueous hydrogen chloride solution. The aqueous layer was washed with isopropyl ether and titrated to pH 8 with saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure. Ethyl acetate and isopropyl ether were added to the residue, and the mixture was stirred at room temperature. The crystals formed were collected by filtration and washed with isopropyl ether. The crystals were dried in vacuo (40 °C) to give 1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (**2**)[3a] (0.39 g, yield 71%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.65 (d, J = 6.8 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H), 2.66−2.74 (m, 1H), 3.84 (s, 3 H), 6.97 (s, 1 H), 7.10 (dd, J = 8.9 and 2.4 Hz, 1 H), 7.22 (d, J = 2.1 Hz, 1 H), 7.53 (s, 1 H), 7.65−7.77 (m, 3 H), 7.99 (s, 1 H); MS (FAB): m/z = 297 (MH^+).

Synthetic Procedure for 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (2) from 9. THF (620 mL) was added to magnesium (26.9 g, 1.11 mol) under a nitrogen atmosphere. Iodine (0.28 g) was added, and the mixture was stirred. While the mixture was kept at less than 50 °C, a solution of 2-bromo-6-methoxynaphthalene (250 g, 1.05 mol) in THF (730 mL) was added dropwise, and the mixture was stirred at 15−25 °C for 1 h. A solution of 1-(1*H*-imidazol-4(5)-yl)-2-methylpropan-1-one (**9**) (51.9 g, 0.376 mol) in THF (370 mL) was added dropwise at 0 °C, and the mixture was stirred at 15−25 °C for 4 h. Saturated aqueous sodium hydrogen carbonate (250 mL) and water (250 mL) were successively added dropwise. After partitioning, the aqueous layer was extracted with ethyl acetate (300 mL). The organic layers were combined, and the mixture was washed with brine and concentrated under reduced pressure. The concentration residue was broken up with ethyl acetate (310 mL) and isopropyl ether (620 mL), and the crystals were collected by filtration and washed with isopropyl ether (620 mL). The crystals were dried in vacuo (40 °C) to give 1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (**2**)[3a] (93.5 g, yield 84%).

Large-Scale Improved Preparation of 1-(6,7-Dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (2). To a solution of 4(5)-imidazolecarboxyaldehyde (**7**) (200 g, 2.08 mol) in pyridine (600 mL) was added hydroxylamine hydrochloride (162 g, 2.33 mol). After the mixture stirred for 2 h at 25−55 °C, acetic anhydride (369 mL, 3.91 mol) was added dropwise at 55−135 °C. The mixture was further stirred until the temperature reached room temperature and was titrated to pH 8 with 30% aqueous sodium hydroxide solution. Ethyl acetate (800 mL) was added for extraction, and the aqueous layer was extracted again with ethyl acetate (800 mL). The organic layers were combined, washed with brine (×2), and concentrated under reduced pressure. Toluene (300 mL) was added to the residue, and the mixture was concentrated under reduced pressure (twice) to give crude 4(5)-cyanoimidazole (**10**) (185 g). A Grignard reagent was prepared from isopropylbromide (598 mL, 6.37 mol), magnesium (163 g, 6.69 mol), and I_2 (1.6 g, 6.37 mmol) in THF (6.4 L). A solution of 4(5)-cyanoimidazole (**10**) (185 g) in THF (1.9 L) was added dropwise over 30 min to the solution of isopropylmagnesium bromide in THF below 0 °C under a nitrogen atmosphere. The mixture was stirred at rt for 3 h. Water (1.9 L) and 10% aqueous sulfuric acid solution (3.8 L) were added dropwise, and the mixture was stirred at 90 min and titrated to pH 8 with 30% aqueous sodium hydroxide solution. After the organic layer was separated, the organic layer was washed with brine and concentrated under reduced pressure. Toluene (2 L) was added to the residue, and the mixture was concentrated under reduced pressure (twice) to give 1-(1*H*-imidazol-4(5)-yl)-2-methylpropan-1-one (**9**) (286 g). THF (3.3 L) was added to magnesium (142 g, 5.85 mol) under a nitrogen atmosphere. Iodine (1.4 g) was added, and the mixture was stirred. While keeping the mixture at less than 50 °C, a solution of 2-bromo-6-methoxynaphthalene (1321 g, 5.57 mol) in THF (3.8 L) was added dropwise, and the mixture was stirred at 15−25 °C for 2 h. A solution of 1-(1*H*-imidazol-4(5)-yl)-2-methylpropan-1-one (**9**) (286 g) in THF (1.9 L) was added dropwise at 0 °C, and the mixture was stirred at 15−25 °C for 3 h. Saturated aqueous sodium hydrogen carbonate (1.4 L) and water (1.4 L) were successively added dropwise. After partitioning, the organic layer was washed with brine and concentrated under reduced pressure. Ethyl acetate (2 L) and isopropyl ether (4 L) were added to the concentration residue, and the mixture was stirred at 25 °C for 2 h. The crystals were collected by filtration and washed with isopropyl ether (1 L). The crystals were dried in vacuo (40 °C) to give 1-(6,7-dimethoxy-2-naphthyl)-1-(1*H*-imidazol-4-yl)-2-methylpropan-1-ol (**2**)[3a] (433 g, yield 70% from **7**).

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