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Catalytic Asymmetric Synthesis of R207910

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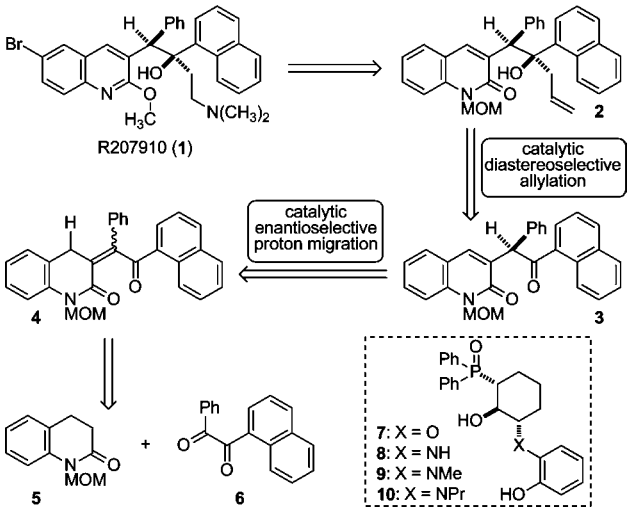
Tuberculosis (TB) is one of the most serious worldwide infectious diseases.[1] Despite the emergence of a multidrug resistant mutant, a new TB drug has not been introduced in the market for more than 40 years. R207910 (**1**), discovered by the Johnson & Johnson pharmaceutical company, is a promising potent anti-TB drug candidate that selectively inhibits the ATP synthase proton pump of both drug-sensitive and drug-resistant *Mycobacterium tuberculosis*.[2] In contrast to its fascinating biological activity, however, the only existing synthetic route of **1** so far reported is rather primitive, involving low-yielding stereorandom C−C bond formation, separation of the desired diastereomer as a minor isomer, and optical resolution using chiral HPLC.[3] In this communication, we describe the first asymmetric synthesis of **1** based on the development of two novel catalytic transformations.

Scheme 1. Retrosynthetic Analysis



The stereocontrolled construction of contiguous tertiary and tetrasubstituted carbons is the greatest challenge in the synthesis of **1**. Our preliminary studies indicated that it was not possible to form the diarylmethyl moiety after construction of the tetrasubstituted carbon. Therefore, we planned to construct the tertiary stereocenter prior to constructing the tetrasubstituted carbon (Scheme 1). We planned to produce enantiomerically enriched ketone **3** from **4**, which can be readily synthesized via a site-selective aldol reaction between **5**[4] and **6**[5] followed by dehydration (75% yield in two steps),[6] through a catalytic enantioselective proton migration reaction. The dimethylaminoethyl moiety of **1** would be introduced to ketone **3** as an allyl group through diastereoselective allylation. Late-stage manipulation (deprotection, bromination, and *O*-methylation) of the quinolinone moiety of **2** would then lead to **1**.

Based on this synthetic plan, we first studied catalytic enantioselective proton migration from **4** to **3**. Late-transition-metal-catalyzed enantioselective olefin migration conditions[7] were not effective in this system. Therefore, we attempted an approach through chiral Brönsted base-catalyzed dienolate formation from **4**, followed by regio- and enantioselective α-protonation. We previously developed a catalytic enantioselective protonation of enol silyl ethers using a gadolinium (Gd) complex derived from ligand *ent*-**7**.[8] In this reaction, chiral Gd enolate species were generated via transmetalation from enol silyl ethers, which were enantioselectively protonated by a proton incorporated in a chiral pentametallic complex, producing enantiomerically enriched ketones with an α-tertiary stereocenter. We initially applied this method to dienol silyl ethers derived from **4**, but even after intensive studies, the enantioselectivity was not satisfactory (up to 63% ee).[6a] Thus, we investigated an enantioselective proton migration reaction from **4** to **3** through a chiral metal dienolate generated via deprotonation, taking advantage of the Brönsted basicity of metal complexes of **7** and related ligands (Table 1).

Table 1. Optimization of Catalytic Enantioselective Proton Migration Reaction

entry	X	ligand	temp (°C)	additive	time (h)	yield (%)	ee[a] (%)
1	30	*ent*-**7**	−20	none	24	>99	50[e]
2	30	*ent*-**8**	−20	none	18	>99	35
3	30	*ent*-**9**	−20	none	5	>99	60[e]
4	30	*ent*-**10**	−20	none	12	>99	24[e]
5	30	**9**	−20	DMAP	3	>99	72
6	10	**9**	−40	DMAP	12	48	83
7	10	**9**	−40	MEPO[b]	8	>99	84
8	10	**9**	−50	MEPO[b]	8	23	86
9	10	**9**	−50	MEPO[b] + Bu_4NCl[c]	24	>99	86
10	2.5	**9**	−50	MEPO[b] + Bu_4NCl[d]	36	>99	88

[a] Determined by chiral HPLC. [b] *p*-Methoxypyridine *N*-oxide. [c] 2 mol % was used. [d] 0.5 mol % was used. [e] The enantiomer of **3** was produced.

Using 30 mol % of a catalyst prepared from $Gd(O^iPr)_3$ and *ent*-**7** in a 1:1.5 ratio,[8] product *ent*-**3** was obtained in quantitative yield with 30% ee (data not shown).[9] Encouraged by this result, we examined various metal sources and obtained *ent*-**3** with 50% ee using a catalyst prepared from yttrium tris(hexamethyldisilazide) [$Y(HMDS)_3$] (Table 1, entry 1). We then modified the structure of the chiral ligands (entries 1−4). Although electronic and steric tuning of the Lewis base (phosphine oxide) and catechol moieties did not improve the enantioselectivity, switching the ether linker of *ent*-**7** to an *N*-methyl group improved the enantiomeric excess to 60% (*ent*-**9**, entry 3).

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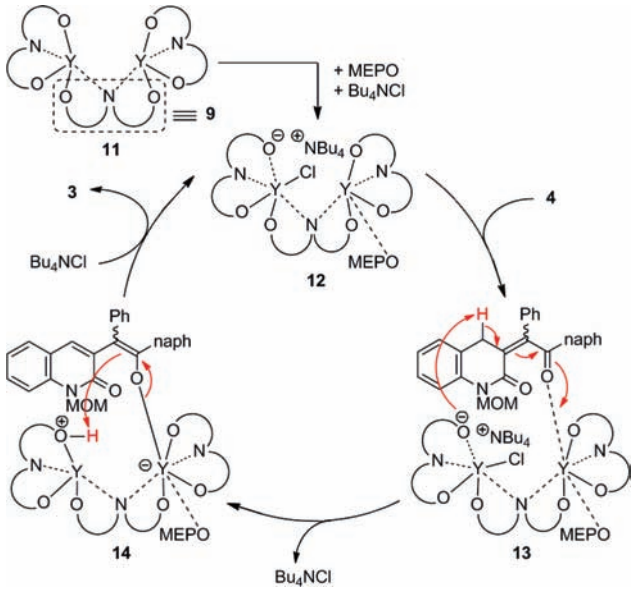
To further improve the enantioselectivity, we evaluated the effects of catalytic additives. Although sulfoxides and phosphine oxides were not beneficial, using various pyridines or *N*-oxides as additives increased the enantioselectivity (entries 5−7 for typical results). In the presence of 10 mol % asymmetric catalyst and 5 mol % *p*-methoxypyridine *N*-oxide (MEPO), **3** was produced with 84% ee at −40 °C (entry 7). At −50 °C, however, the yield of **3** decreased to 23% with a slightly improved 86% ee (entry 8). The use of Bu_4NCl (2 mol %) as a second additive markedly enhanced the reactivity without affecting the enantioselectivity (entry 9). Because Bu_4NCl itself promotes racemic proton migration to some extent,[10] the amount of Bu_4NCl must be much smaller ($\times 1/5$) than the amount of the asymmetric catalyst. Finally, by using 2.5 mol % Y-catalyst, 1.25 mol % MEPO, and 0.5 mol % Bu_4NCl, **3** was obtained in quantitative yield in 36 h with 88% ee (entry 10).[11] Enantiomerically pure **3** was obtained through a single recrystallization of the product from ^{i}PrOH/hexanes =10/1 (43%, not optimized).

Scheme 2. Proposed Model of the Catalytic Cycle

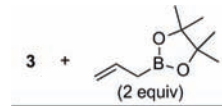


To gain insight into the reaction mechanism, we studied the catalyst composition using ESI-MS.[6a] An MS peak corresponding to Y/**9** = 2:3 complex **11** was predominantly observed in a solution prepared from $Y(HMDS)_3$ and **9** mixed in a 2:3 ratio. In the presence of 0.5 equiv (to Y) of MEPO, MS peaks corresponding to **11** and a Y/**9**/MEPO = 2:3:1 complex were observed. Therefore, the Y/**9**/MEPO = 2:3:1 ternary complex would be the active enantioselective catalyst.[12] This hypothesis was also supported by the observed dependency of the enantioselectivity on the Y/**9** ratio when the catalyst was prepared. Thus, the enantiomeric excess of **3** gradually increased from 80% ee to 86% ee (using 10 mol % catalyst; Table 1, entry 9) according to the increase of the Y/**9** ratio from 1:1 to 1:1.5 and remained consistent at 86% ee from a 1:1.5 to 1:2 ratio.[6a] This dependency again indicated that the active catalyst with optimum enantioselectivity was generated at Y/**9** = 1:1.5 ratio.

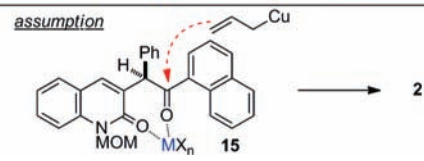
Based on the structural information and the experimental results that additive MEPO increased the enantioselectivity while Bu_4NCl accelerated the reaction without affecting the enantioselectivity, we propose the working model shown in Scheme 2 for the catalytic cycle. MEPO coordinates to one of the Y metals of the bimetallic complex and favorably modifies the asymmetric environment of the catalyst. Meanwhile, Bu_4NCl might increase the Brönsted basicity of the catalyst, by generating an ammonium phenoxide (or alkoxide) moiety in **12**, which would deprotonate **4** via **13**. The thus-generated *pre*-transition state complex **14** contains an active Y-enolate and an acidic proton, both derived from substrate **4**, at defined positions in the complex. Asymmetric α-protonation would proceed in complex **14**, producing enantiomerically enriched **3** and regenerating catalyst **12**.

With enantiomerically pure **3** in hand, we next focused on a diastereoselective construction of the tetrasubstituted carbon through the addition of a carbon nucleophile to ketone **3**. All attempts using conventional nucleophiles, including lithium enolates, metal enolate equivalents derived from acetonitrile, vinyl Grignard reagents, allyl Grignard reagents ± $CeCl_3$, allylindium, allylzinc, and metal alkynides failed due to both the high steric demand and the presence of the fairly acidic α-proton of the ketone carbonyl group. Therefore, we studied the CuF-catalyzed allylboration developed in our group.[13] Generally, this reaction proceeds from a wide range of ketones under mild conditions at approximately neutral pH. As expected, the allylation product was obtained in 48% yield using 20 mol % of CuF•3PPh_3•2EtOH catalyst,[14] despite the fact that the desired diastereomer **2** was the minor isomer with low selectivity (Table 2, entry 1). Although reactions in the presence of previously identified rate-accelerating additives such as La(O^iPr)$_3$ and LiO^iPr did not afford the allylation product (entries 2−3), the yield was markedly improved in the presence of 30 mol % KO^tBu (entry 4). The diastereoselectivity, however, remained unchanged.

Table 2. Optimization of Catalytic Diastereoselective Allylation



entry	X	additives (mol %)	yield (%)[a]	d.r.[b]
1	20	none	48	1/1.2
2	20	La(O^iPr)$_3$ (30)	0[c]	–
3	20	LiO^iPr (30)	0[d]	–
4	20	KO^tBu (30)	> 99	1/1.2
5	20	KO^tBu (30), Ti(O^iPr)$_4$ (100)	67	1/1.2
6	20	KO^tBu (30), $MgCl_2$ (100)	> 99	1.2/1
7	20	KO^tBu (30), $ZnCl_2$ (100)	> 99	2.2/1
8	20	KO^tBu (30), $ZnCl_2$ (100), TBAT (100)	75	3.4/1
9[e]	10	KO^tBu (15), $ZnCl_2$ (100), Bu_4PBF_4 (100)	> 99	14/1
10	1	KO^tBu (1.5), $ZnCl_2$ (100), Bu_4PBF_4 (100)	95	5.6/1



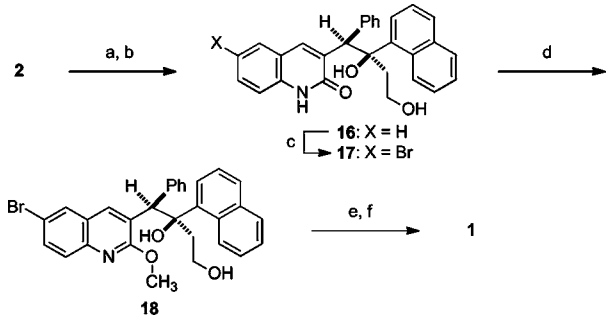
[a] Combined yield of two diastereomers. [b] Diastereomeric ratio of **2**/undesired isomer. [c] Complex mixture was produced. [d] No reaction. [e] Reaction time was 1 h. In other entries, reaction time was 24 h.

To improve the diastereoselectivity, we assumed that the desired isomer **2** would be produced by forming a seven-membered chelate **15** and introducing an allyl group from the less hindered α-side.[15] Based on this assumption, we studied the effects of oxophilic metal additives (entries 5−7). Diastereoselectivity was slightly improved in the presence of a stoichiometric amount of $ZnCl_2$ (entry 7). Extensive studies revealed that the diastereoselectivity was further improved to 3.4/1 by adding a fluoride source, TBAT ($Bu_4NPh_3F_2Si$: entry 8). Thus, potential fluoride sources were screened next to identify the optimized conditions (entry 9); using 10 mol % CuF•3PPh_3•2EtOH, 15 mol % KO^tBu, 1 equiv of $ZnCl_2$, and 1 equiv of Bu_4PBF_4, the reaction was completed after 1 h at room

temperature, affording the product in quantitative yield with a diastereomeric ratio of 14/1.[16] The reaction could be performed using 1 mol % of the Cu catalyst (24 h), but the diastereoselectivity diminished to 5.6/1 (entry 10). Further, we confirmed that no epimerization of the tertiary chiral center occurred during this allylation reaction.

Having established the catalytic asymmetric route to enantiomerically pure key intermediate **2**, the remaining tasks included converting the allyl group to a dimethylaminoethyl group and the protected quinolinone moiety to a brominated methoxyquinoline (Scheme 3). After cleaving the *N*-methoxymethyl (MOM) group, ozonolysis followed by reductive treatment produced diol **16**. Regioselective bromination of **16** with NBS proceeded in 83% yield in the presence of buffering NaOAc. The use of DMF as a solvent was critical in this conversion. Selective *O*-methylation of **17** was problematic because the substrate contained undesired competitive nucleophilic sites. Although most of the attempted combinations of bases and methylating reagents produced undesired *N*-methylated products, a combination of Ag_2CO_3 and MeI[17] selectively produced the desired *O*-methylation product. In this case, however, overmethylation occurred at the primary alcohol oxygen atom. This side reaction was effectively suppressed by adding a dummy substrate, EtOH, to the reaction mixture. Thus, the desired product **18** was obtained in 63% yield. Finally, *O*-tosylation followed by substitution with Me_2NH afforded R207910 (**1**). The spectroscopic data of synthetic **1** were consistent with the reported data in all aspects,[3,18] including the optical rotation ($[\alpha]^{26}_D = -168.0$ ($c = 0.3$, DMF), ref.: $[\alpha]^{20}_D = -166.98$ ($c = 0.5$, DMF)[3]).

Scheme 3. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) *B*-bromobenzodioxaborole, CH_2Cl_2, 83%. (b) O_3, MeOH/H_2O; $NaBH_4$, 74%. (c) NBS, NaOAc, DMF, 83%. (d) MeI, Ag_2CO_3, EtOH, CH_3CN, 63%. (e) TsCl, DMAP, py, 90%. (f) Me_2NH, DMF, H_2O, 62%.

In conclusion, we achieved the first asymmetric synthesis of R207910 by developing two key catalytic transformations: a catalytic enantioselective proton migration reaction of **4** to **3** using a bimetallic Y-complex and a CuF-catalyzed diastereoselective allylation of ketone **3** to **2**. This synthesis includes 12 of the longest linear steps from commercially available materials[6a] with an overall yield of 5%. Further improvement of the synthetic efficiency and elucidation of the mechanism of the two key catalytic reactions are currently ongoing.

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Supporting Information Available: Experimental procedures, characterization of the products, ESI-MS studies of the Y-catalyst composition, and a proposed catalytic cycle of CuF-catalyzed allylation of **3**. Complete ref 2a was also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) See Supporting Information (SI). (b) Only a single set of ^1H and ^{13}C NMR signals was observed for **4** at room temperature, possibly due to rapid *E*/*Z* isomerization of the double bond.
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(9) Enone **4** gradually converted to **3**, even in the absence of any catalyst at room temperature, indicating that **3** is thermodynamically more stable than **4**.
(10) Racemic **3** was produced from **4** in 33% yield in the presence of 2 mol % of Bu_4NCl (in the absence of an asymmetric catalyst) at −50 °C for 60 h.
(11) It was confirmed that no racemization of **3** occurred during the reaction time course under the optimized conditions.
(12) (a) The peak corresponding to the ternary complex was not observed in the presence of Bu_4NCl. Instead, binary complex **11** was the predominant species. Nonetheless, we assume that the ternary complex is the actual catalyst based on the fact that enantioselectivity was significantly increased in the presence of MEPO. (b) ESI-MS provided valid structural information for the related rare earth metal catalysts. For example, see: Kato, N.; Mita, T.; Kanai, M.; Therrien, B.; Kawano, M.; Yamaguchi, K.; Danjo, H.; Sei, Y.; Sato, A.; Furusho, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6768.
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(14) (a) Gulliner, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153. (b) The constitutional crystalline solvent EtOH was essential for the promotion of this reaction.
(15) Attempts to improve the diastereoselectivity through chiral ligand control were not successful. In the presence of chiral bisphosphines, unexpected α-C−$C_{carbonyl}$ bond cleavage subsequent to the allyl addition to the ketone occurred.
(16) (a) Preliminary studies using ^{11}B and ^{19}F NMR suggested that ZnFCl and Bu_4PBF_3Cl might be generated from the additives. A ZnFCl species would have higher Lewis acidity than $ZnCl_2$, which might be beneficial for the improvement of the diastereoselectivity by favorably forming chelate **15**. (b) For a proposed catalytic cycle of this allyboration including possible roles of additives, see SI.
(17) For examples of *O*-methylation of quinolinone derivatives using Ag_2CO_3 as a base, see: (a) Morel, A. F.; Larghi, E. L.; Selvero, M. M. *Synlett* **2005**, 2755. (b) Bodendiek, S. B.; Mahieux, C.; Hänsel, W.; Wulff, H. *Eur. J. Med. Chem.* **2009**, *44*, 1838.
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