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Ruthenium-Catalyzed Highly Enantioselective Synthesis of *cis*-3-Quinuclidinols via DKR Asymmetric Transfer Hydrogenation

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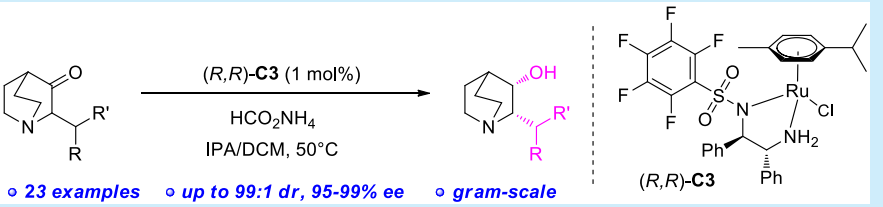

ABSTRACT: A method for the enantioselective synthesis of *cis*-3-quinuclidinols by Ru-catalyzed asymmetric transfer hydrogenation via dynamic kinetic resolution is described. The reaction proceeded under mild conditions using ammonium formate as the hydrogen donor, affording the products in high yields (up to 99%) with excellent diastereoselectivity (up to 99:1 dr) and enantioselectivity (95−99% ee). This protocol was applicable to gram-scale preparation with perfect enantioselectivity through simple recrystallization.

Chiral quinuclidines are important structural motifs prevalently found in biologically active compounds and natural products.[1] In particular, optically active 3-quinuclidinols constitute one of the common pharmacophoric elements in drug discovery (Figure 1).[2] Representative examples include

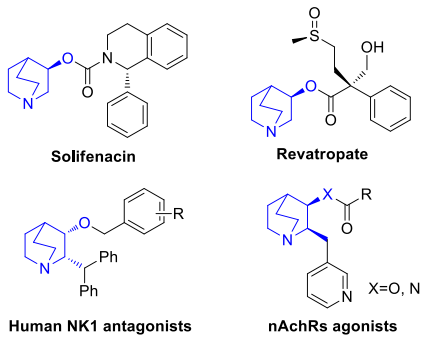

Figure 1. Selected biologically active compounds containing chiral quinuclidine moieties.

antimuscarinic agents, solifenacin[2c] and revatropate,[2d] which were developed as potential treatments of chronic obstructive pulmonary disease (COPD). Moreover, chiral 2-substituted-3-quinuclidinols are also the key synthetic intermediates of a variety of bioactive compounds.[3]

Great efforts have been devoted to the pursuit of an efficient synthetic route toward chiral quinuclidinols. These approaches including asymmetric hydrogenation,[4] enzymatic resolution,[5] and biocatalytic reduction.[6] Compared to the well-established methodologies toward (*R*)-3-quinuclidinol, limited reports are available regarding the enantioselective synthesis of 2-substituted quinuclidinols having two stereogenic centers. Furthermore, asymmetric hydrogenation of bicyclic ketones is challenging due to (1) the sterically congested and rigid [2.2.2] cyclooctane skeleton and (2) the precise discrimination between alkyl groups,[7a] which is consistent with the fact that only a few successful examples have been reported.[7] In 2010, Ohkuma and co-workers reported the efficient asymmetric hydrogenation (AH) of 3-quinuclidinones using a combined catalyst system of $RuCl_2$[(*S*)-binap][(*R*)-iphan] and *t*-BuOK, which exhibited good diastereo- and enantioselectivity for 2-diphenylmethyl-3-quinuclidinone, but only one example was disclosed (Scheme 1a).[7a] Another report from a patent described the enantioselective synthesis of 2-arylmethyl-3-quinuclidinols with moderate enantioselectivities (85−93% ee).[7b] Therefore, the development of a modular asymmetric catalytic methodology for the preparation of a wide range of *cis* quinuclidinols bearing different substituents at the 2-position is still highly desirable.

Asymmetric transfer hydrogenation of ketones via DKR has proved to be one of the most direct and reliable methods to

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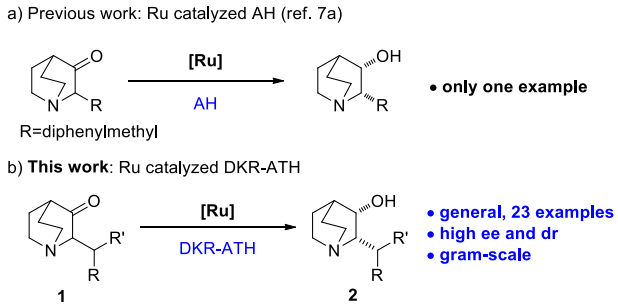
Scheme 1. Asymmetric Catalytic Synthesis of 3-Quinuclidinols

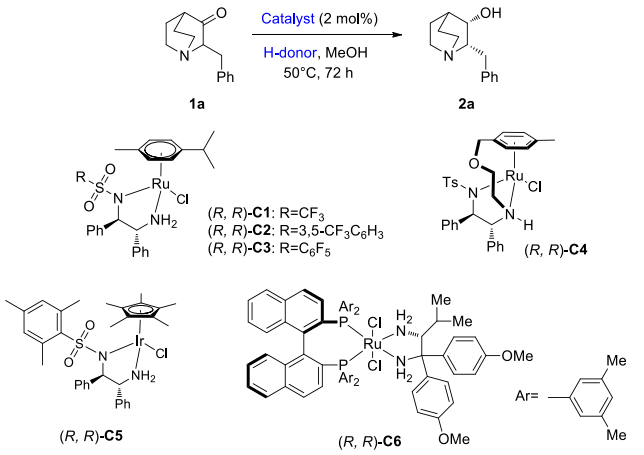


produce optically active alcohols.[8,9] An ongoing interest in our laboratory is the use of chiral diamine−Ru complexes as catalysts for the construction of chiral compounds typically found in pharmaceuticals.[10] In light of this previous work, we envisioned that the two contiguous stereogenic centers in quinuclidinol could be established in one operation via DKR-ATH. We herein report the successful efficient synthesis of *cis*-3-quinuclidinols bearing diverse functionalized substituents at the 2-position (Scheme 1b).

We set out to examine ATH of quinuclidinones using **1a** as the model substrate (Table 1). Initially, several commonly used Ru−diamine complexes such as tethered Ru catalyst (*R,R*)-**C4**,[11] were screened with HCO_2H/Et_3N as hydrogen donor (entries 1−4). Although quantitative conversions were achieved in almost all cases, most of them afforded only low-to-moderate enantioselectivities. An exception to this transformation was (*R,R*)-**C1**, which provided good enantiocontrol; however, low diastereoselectivity was also observed (entry 1). It was shown that hydrogen donors played an important role in the selectivity of transfer hydrogenation (entries 1 and 5). This observation intrigued us to evaluate other hydrogen donors in combination with different catalysts. Gratifyingly, a good enantio- and diastereoselectivity was achieved using ammonium formate as the hydrogen donor in the presence of (*R,R*)-**C3** (>20:1 dr, 94% ee entry 7). It should be noted that (*R,R*)-**C6** provided a good enantioselectivity, while the diastereoselectivity was poor (8:1 dr, 94% ee, entry 10).

Subsequently, further condition optimization, including solvent effect and catalyst loading, is summarized in Table 2.

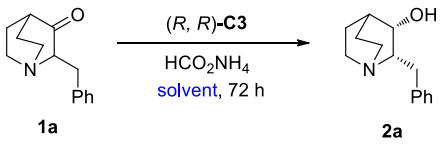
Table 1. Screening of Catalysts and H-Source for ATH of 3-Quinuclidinone 1a[a]



entry	catalyst	H donor	conv[b] (%)	dr[c]	ee[c] (%)
1[d]	(*R, R*)-**C1**	HCO_2H/Et_3N	98	14:1	91
2[d]	(*R, R*)-**C2**	HCO_2H/Et_3N	>99	98:2	63
3[d]	(*R, R*)-**C3**	HCO_2H/Et_3N	>99	99:1	66
4[d]	(*R, R*)-**C4**	HCO_2H/Et_3N	>99	99:1	75
5[e]	(*R, R*)-**C1**	HCO_2NH_4	>99	>99:1	88
6[e]	(*R, R*)-**C2**	HCO_2NH_4	>99	>99:1	91
7[e]	**(*R, R*)-C3**	**HCO_2NH_4**	**>99**	**>99:1**	**94**
8[e]	(*R, R*)-**C4**	HCO_2NH_4	>99	>99:1	90
9[e]	(*R, R*)-**C5**	HCO_2NH_4	>99	16:1	31
10[f]	(*R, R*)-**C6**	IPA/*t*-BuOK	85	8:1	94

[a]General conditions: **1a** (0.5 mmol), catalyst (2.0 mol %), and H-donor in the solvent (20 mL) at 50 °C for 72 h. [b]Determined by HPLC. [c]Determined by chiral HPLC using a Daicel Chiralpak IE column. [d]HCO_2NH_4 (5.0 equiv), MeOH used as a solvent. [e]HCO_2H/Et_3N (5:2, 1.6 mmol); DCM used as a solvent. [f]H_2 (5 MPa), *t*-BuOK in IPA (1 M, 0.1 equiv).

Table 2. Further Optimization of Reaction Conditions[a]



entry	S/C	solvent	conv[b] (%)	dr[c]	ee[c] (%)
1	50	DCM	trace	ND	ND
2	50	EA	trace	ND	ND
3	50	MeCN	87	99:1	95
4	50	IPA	>99	>99:1	98
5	50	MeOH/DCM	>99	>99:1	97
6	50	IPA/DCM	>99	>99:1	>99
7	50	IPA/DCE	>99	>99:1	97
8	**100**	**IPA/DCM**	**>99**	**>99:1**	**>99**
9[d]	200	IPA/DCM	97	>99:1	98
10[d]	500	IPA/DCM	95	>99:1	96

[a]Conditions: the reaction was performed with **1a** (0.2 mmol), HCO_2NH_4 (5.0 equiv), and catalyst (*R, R*)-**C3** in 2.0 mL of solvent at 50 °C for 72 h. [b]Determined by HPLC. [c]Determined by chiral HPLC using a CHIRALPAK IA column. [d]The reaction was carried out on 70 °C. ND = not detected.

Extensive screening of solvents revealed their significant effect on enantiocontrol. Isopropyl alcohol (IPA) provided a full conversion and excellent enantioselectivity (98% ee, entry 4), while aprotic solvents such as dichloromethane (DCM) and ethyl acetate (EA) led to poor results (entries 1 and 2). The best result was obtained using the mixture solvents of IPA/DCM (v/v = 1:1) (>20:1, >99% ee, entry 8). Moreover, lowering the catalyst loading of (*R,R*)-**C3** resulted in slightly decrease in enantioselectivities and conversions at 70 °C but did not deteriorate the diastereomeric ratios (entries 9 and 10). In addition, equivalents of HCO_2NH_4 and reaction temperature were also evaluated (see Tables S2 and S3 for details). Therefore, the best result was generally obtained when the reaction was catalyzed by (*R,R*)-**C3** (1.0 mol %) using HCO_2NH_4 as the hydrogen donor and IPA/DCM (v/v = 1:1) as the solvent at 50 °C for 72 h.

Under the optimal conditions, the scope of 2-arylmethyl-3-quinuclidinones was examined (Scheme 2). In general, all of the substrates (**1a−s**) could be successfully hydrogenated to afford the desired products **2a−s** in quantitative conversions and with excellent diastereo- and enantioselectivities (up to

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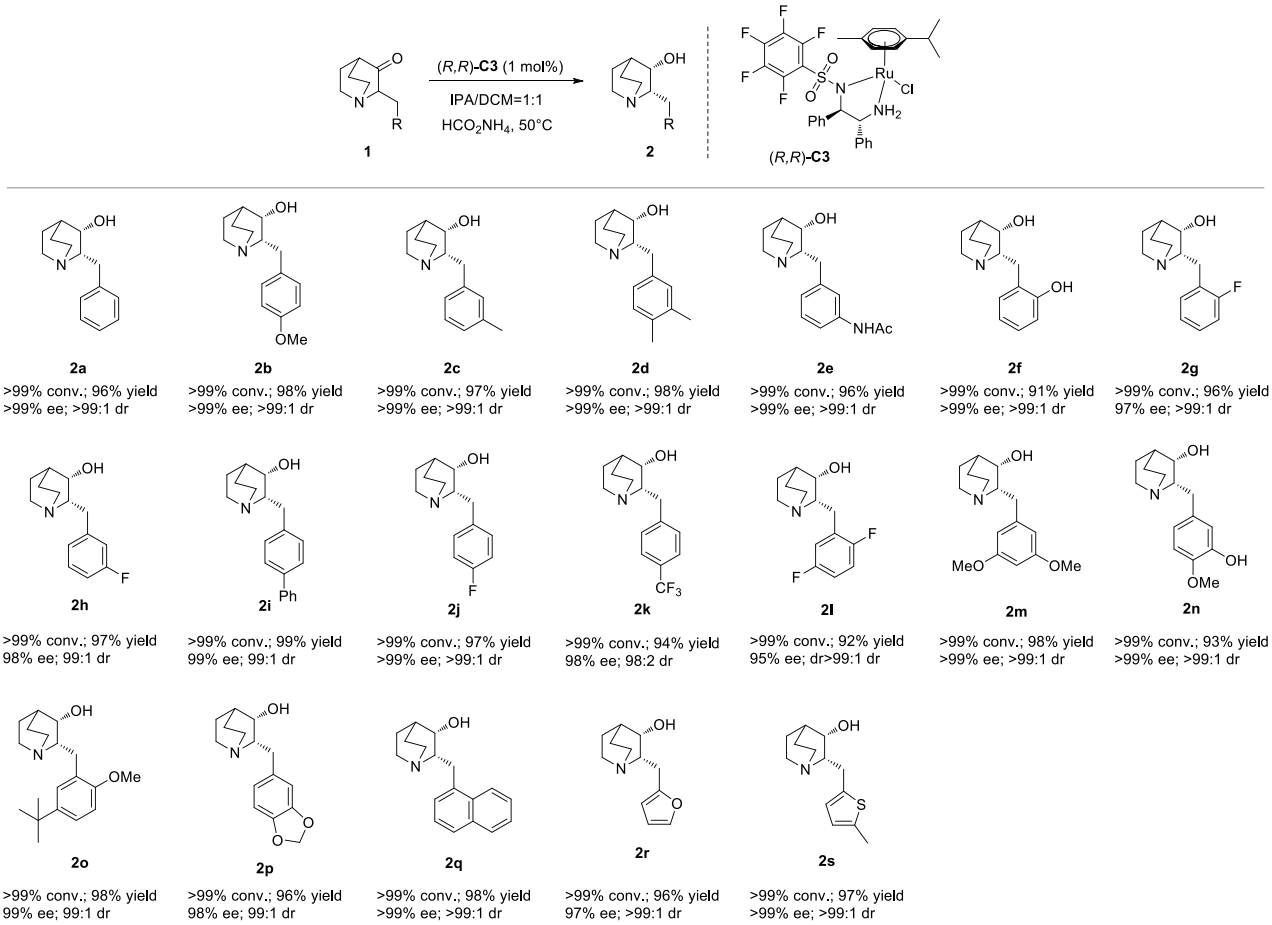
Scheme 2. DKR-ATH of 3-Quinuclidinone 1a–s Catalyzed by (*R, R*)-C3[a]

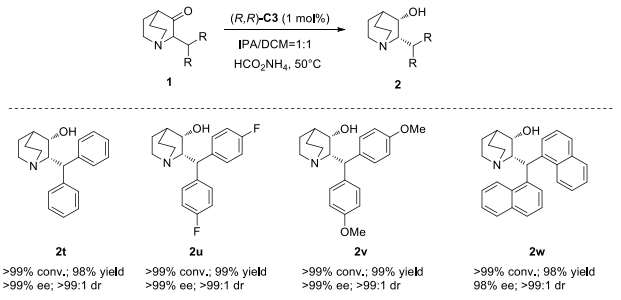


[a]Reaction conditions: **1** (1.2 mmol), HCO_2NH_4 (6.0 mmol), (*R, R*)-**C3** (1.0 mol %), IPA/DCM (20 mL, 1:1), at 50 °C for 72 h. Isolated yields ee values and dr ratios were determined by chiral HPLC analysis of the crude reaction mixture.

99:1 dr and 99% ee). Neither the position nor electronic properties of the substituents at the phenyl ring of the substrates had an apparent effect on the reactivity and selectivity. Notably, substrates with electron-withdrawing substituents including the F, CF_3 groups displayed relatively lower enantioselectivity compared with those bearing electron-donating substituents. For instance, the fluoro- or difluoro-substituted substrates (**1g**, **1h**, **1l**) were hydrogenated with 96–97% ee, while the substrates bearing electron-donating substituents Me, MeO (**1b–d**) provided >99% ee. Remarkably, heteroaromatic substrates, such as **1r** and **1s**, were also compatible for this transformation to afford the products **2r** and **2s** with 97% and >99% ee, respectively. Furthermore, 2-diarylmethyl-3-quinuclidinones were also evaluated in the optimized protocol. As shown in Scheme 3, all of the examined substrates (**1t–w**) were reduced in almost full conversion with excellent levels of diastereoselectivity (>99:1 dr) and enantioselectivity (98–99% ee).

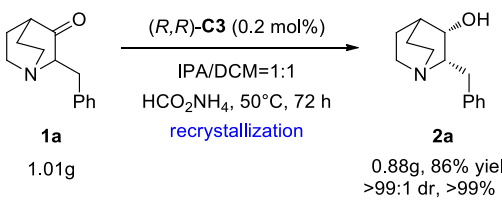
With the general scope of the transformation established, we sought to demonstrate the synthetic utility of this methodology. A gram-scale synthesis of **2a** was performed with a decreased catalyst loading (Scheme 4). The reaction proceeded smoothly with quantitative conversion at 50 °C over 72 h, affording the desired product **2a** with >99% ee and >99:1 dr without any decrease of enantioselectivity. The

Scheme 3. DKR-ATH of 3-Quinuclidinone 1t–w Catalyzed by (*R, R*)-C3[a]



[a]Reaction conditions: **1** (1.2 mmol), HCO_2NH_4 (6.0 mmol), (*R,R*)-**C3** (1.0 mol %), IPA/DCM (20 mL, 1:1), at 50 °C for 72 h. Isolated yields ee values and dr ratios were determined by chiral HPLC analysis of the crude reaction mixture.

Scheme 4. Gram-Scale Synthesis of 2a



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optically pure **2a** could be further recrystallized from IPA/hexane in 86% isolated yield.

In conclusion, we have developed a highly efficient method for enantioselective synthesis of *cis*-3-quinuclidinols via Ru-catalyzed DKR asymmetric transfer hydrogenation. The products are efficiently accessed in good yields and excellent diastereo- and enantioselectivities (up to 99:1 dr, 95−99% ee) catalyzed by in-house developed Ru−diamine complexes using ammonium formate as the hydrogen donor. This mild and operationally simple method provides an alternative route to *cis* 2-substituted-3-quinuclidinols and expands the scope for asymmetric transfer hydrogenation of bicyclic ketones. Furthermore, the practical utility of this method was demonstrated by the efficient gram-scale asymmetric transfer hydrogenation of **1a** with perfect enantioselectivity through simple recrystallization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01361.

Optimization tables, experimental procedure, and characterization data for all of the substrates and products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Uskokovic, M. R.; Grethe, G. *The Cinchona Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. *14*. (b) Kaufman, T. S.; Ruveda, E. A. The quest for quinine: those who won the battles and those who won the war. *Angew. Chem., Int. Ed.* **2005**, *44*, 854−85. (c) Kurasawa, O.; Miyazaki, T.; Homma, M.; Oguro, Y.; Imada, T.; Uchiyama, N.; Iwai, K.; Yamamoto, Y.; Ohori, M.; Hara, H.; Sugimoto, H.; Iwata, K.; Skene, R.; Hoffman, I.; Ohashi, A.; Nomura, T.; Cho, N. Discovery of a novel, highly potent, and selective thieno[3,2-d]pyrimidinone-based Cdc7 Inhibitor with a quinuclidine moiety (TAK-931) as an orally active investigational antitumor agent. *J. Med. Chem.* **2020**, *63*, 1084−1104.

(2) (a) Prat, M.; Fernandez, D.; Buil, M. A.; Crespo, M. I.; Casals, G.; Ferrer, M.; Tort, L.; Castro, J.; Monleon, J. M.; Gavalda, A.; Miralpeix, M.; Ramos, I.; Domenech, T.; Vilella, D.; Anton, F.; Huerta, J. M.; Espinosa, S.; Lopez, M.; Sentellas, S.; Gonzalez, M.; Alberti, J.; Segarra, V.; Cardenas, A.; Beleta, J.; Ryder, H. Discovery of novel quaternary ammonium derivatives of (3*R*)-quinuclidinol esters as potent and long-acting muscarinic antagonists with potential for minimal systemic exposure after inhaled administration: identification of (3*R*)-3-{[hydroxy(di-2-thienyl)acetyl]oxy}-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2 0.2]octane bromide (aclidinium bromide). *J. Med. Chem.* **2009**, *52*, 5076−92. (b) Fischer, O.; Hofmann, J.; Rampp, H.; Kaindl, J.; Pratsch, G.; Bartuschat, A.; Taudte, R. V.; Fromm, M. F.; Hübner, H.; Gmeiner, P.; Heinrich, M. R. Regiospecific introduction of halogens on the 2-aminobiphenyl subunit leading to highly potent and selective M3 muscarinic acetylcholine receptor antagonists and weak inverse agonists. *J. Med. Chem.* **2020**, *63*, 4349. (c) Naito, R.; Yonetoku, Y.; Okamoto, Y.; Toyoshima, A.; Ikeda, K.; Takeuchi, M. Synthesis and antimuscarinic properties of quinuclidin- 3-yl 1, 2, 3, 4-tetrahydroisoquinoline-2-carboxylate derivatives as novel muscarinic receptor antagonists. *J. Med. Chem.* **2005**, *48*, 6597−6606. (d) Montuschi, P.; Ciabattoni, G. Bronchodilating drugs for chronic obstructive pulmonary disease: current status and future trends. *J. Med. Chem.* **2015**, *58*, 4131−4164.

(3) (a) Warawa, E. J.; Mueller, N. J.; Jules, R. Quinuclidine chemistry. 2. Synthesis and antiinflammatory properties of 2-substituted benzhydryl-3-quinuclidinols. *J. Med. Chem.* **1974**, *17*, 497−501. (b) Kubo, I.; Muroi, H.; Masaki, H.; Kubo, A. Antibacterial activity of long-chain alcohols: the role of hydrophobic alkyl groups. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1305−1308. (c) Swain, C. J.; Sewart, E. M.; Cascieri, M. A.; Fong, T. M.; Herbert, R.; MacIntyre, D. E.; Merchant, K. J.; Owen, S. N.; Owens, A. P. Identification of a series of 3-(benzyloxy)-1-azabicyclo[2.2.2]octane human NK1 antagonists. *J. Med. Chem.* **1995**, *38*, 4793−4805. (d) Mazurov, A.; Klucik, J.; Miao, L.; Phillips, T. Y.; Seamans, A.; Schmitt, J. D.; Hauser, T. A.; Johnson, R. T.; Miller, C. 2-(Arylmethyl)-3-substituted quinuclidines as selective α7 nicotinic receptor ligands. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2073−2077.

(4) (a) Ito, T.; Aoki, T. PCT Int. WO 2004078686 A1, 2004. (b) Tsutsumi, K.; Katayama, T.; Utsumi, N.; Murata, K.; Arai, N.;

Kurono, N.; Ohkuma, T. Practical asymmetric hydrogenation of 3-quinuclidinone catalyzed by the XylSkewphos/PICA-Ruthenium(II) complex. *Org. Process Res. Dev.* **2009**, *13*, 625−628.
(5) Nomoto, F.; Hirayama, Y.; Ikunaka, M.; Inoue, T.; Otsuka, K. A practical chemoenzymatic process to access (*R*)-quinuclidin-3-ol on scale. *Tetrahedron: Asymmetry* **2003**, *14*, 1871−1877.
(6) (a) Zhang, W.-X.; Xu, G.-C.; Huang, L.; Pan, J.; Yu, H.-L.; Xu, J.-H. Highly efficient synthesis of (*R*)-3-quinuclidinol in a space-time yield of 916 g L^{-1} d^{-1} using a new bacterial reductase ArQR. *Org. Lett.* **2013**, *15*, 4917−4919. (b) Chen, Q.; Xie, B.; Zhou, L.; Sun, L.; Li, S.; Chen, Y.; Shi, S.; Li, Y.; Yu, M.; Li, W. A tailor-made self-sufficient whole-cell biocatalyst enables scalable enantioselective synthesis of (*R*)-3-quinuclidinol in a high space-time yield. *Org. Process Res. Dev.* **2019**, *23*, 1813−1821.
(7) (a) Arai, N.; Akashi, M.; Sugizaki, S.; Ooka, H.; Inoue, T.; Ohkuma, T. Asymmetric hydrogenation of bicyclic ketones catalyzed by BINAP/IPHAN−Ru(II) complex. *Org. Lett.* **2010**, *12*, 3380−3383. (b) Katayama, T.; Murata, K., U.S. Patent US 20080081911 A1, 2008.
(8) For selected reviews, see: (a) Noyori, R.; Hashiguchi, S. Asymmetric transfer hydrogenation catalyzed by chiral ruthenium complexes. *Acc. Chem. Res.* **1997**, *30*, 97−102. (b) Wang, D.; Astruc, D. The golden age of transfer hydrogenation. *Chem. Rev.* **2015**, *115*, 6621−86. (c) Seo, C. S. G.; Morris, R. H. Catalytic homogeneous asymmetric hydrogenation: successes and opportunities. *Organometallics* **2019**, *38*, 47−65. (d) Barrios-Rivera, J.; Xu, Y.; Wills, M. Applications of N'-monofunctionalised TsDPEN derivatives in asymmetric catalysis. *Org. Biomol. Chem.* **2019**, *17*, 1301−1321.
(9) (a) Hannedouche, J.; Clarkson, G. J.; Wills, M. A new class of "tethered" Ruthenium(II) catalyst for asymmetric transfer hydrogenation reactions. *J. Am. Chem. Soc.* **2004**, *126*, 986−987. (b) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. A class of Ruthenium(II) catalyst for asymmetric transfer hydrogenations of ketones. *J. Am. Chem. Soc.* **2005**, *127*, 7318−7319. (c) Touge, T.; Kuwana, M.; Komatsuki, Y.; Tanaka, S.; Nara, H.; Matsumura, K.; Sayo, N.; Kashibuchi, Y.; Saito, T. Development of asymmetric transfer hydrogenation with a bifunctional oxo-tethered ruthenium catalyst in flow for the synthesis of a ceramide (d-erythro-CER[NDS]). *Org. Process Res. Dev.* **2019**, *23*, 452−461. (d) He, B.; Phansavath, P.; Ratovelomanana-Vidal, V. Rh-mediated asymmetric-transfer hydrogenation of 3-substituted chromones: a route to enantioenriched *cis*-3-(hydroxymethyl)chroman-4-ol derivatives through dynamic kinetic resolution. *Org. Lett.* **2019**, *21*, 3276−3280. (e) Touge, T.; Sakaguchi, K.; Tamaki, N.; Nara, H.; Yokozawa, T.; Matsumura, K.; Kayaki, Y. Multiple absolute stereocontrol in cascade lactone formation via dynamic kinetic resolution driven by the asymmetric transfer hydrogenation of keto acids with oxo-tethered ruthenium catalysts. *J. Am. Chem. Soc.* **2019**, *141*, 16354−16361. (f) Wang, F.; Zheng, L.-S.; Lang, Q.-W.; Yin, C.; Wu, T.; Phansavath, P.; Chen, G.-Q.; Ratovelomanana-Vidal, V.; Zhang, X. Rh(III)-catalyzed diastereoselective transfer hydrogenation: an efficient entry to key intermediates of HIV protease inhibitors. *Chem. Commun.* **2020**, *56*, 3119−3122.
(10) (a) Sun, G.; Zhou, Z.; Luo, Z.; Wang, H.; Chen, L.; Xu, Y.; Li, S.; Jian, W.; Zeng, J.; Hu, B.; Han, X.; Lin, Y.; Wang, Z. Highly enantioselective synthesis of syn-β-hydroxy α-dibenzylamino esters via DKR asymmetric transfer hydrogenation and gram-scale preparation of Droxidopa. *Org. Lett.* **2017**, *19*, 4339−4342. (b) Luo, Z.; Sun, G.; Zhou, Z.; Liu, G.; Luan, B.; Lin, Y.; Zhang, L.; Wang, Z. Stereogenic *cis*-2-substituted-N-acetyl-3-hydroxy-indolines via ruthenium(ii)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation. *Chem. Commun.* **2018**, *54*, 13503−13506. (c) Sun, G.; Jian, W.; Luo, Z.; Sun, T.; Li, C.; Zhang, J.; Wang, Z. Development of an efficient and scalable asymmetric synthesis of eliglustat via Ruthenium(II)-catalyzed asymmetric transfer hydrogenation. *Org. Process Res. Dev.* **2019**, *23*, 1204−1212.
(11) (a) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. Oxo-tethered Ruthenium(II) complex as a bifunctional catalyst for asymmetric transfer hydrogenation and H_2 hydrogenation. *J. Am. Chem. Soc.* **2011**, *133*, 14960−14963. (b) Parekh, V.; Ramsden, J. A.; Wills, M. Ether-tethered Ru(II)/TsDPEN complexes; synthesis and applications to asymmetric transfer hydrogenation. *Catal. Sci. Technol.* **2012**, *2*, 406−414. (c) Nedden, H. G.; Zanotti-Gerosa, A.; Wills, M. The Development of phosphine-free "tethered" Ruthenium(II) catalysts for the asymmetric reduction of ketones and imines. *Chem. Rec.* **2016**, *16*, 2623−2643.

https://dx.doi.org/10.1021/acs.orglett.0c01361
Org. Lett. XXXX, XXX, XXX−XXX