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DOI: 10.1039/C9CC09793G

Rh(III)-Catalyzed Diastereoselective Transfer Hydrogenation: an Efficient Entry to Key Intermediates of HIV Protease Inhibitors

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A highly efficient diastereoselective transfer hydrogenation of α-aminoalkyl α'-chloromethyl ketones catalyzed by a tethered rhodium complex was developed and successfully utilized in the synthesis of the key intermediates of HIV protease inhibitors. With the current Rh(III) catalyst system, a series of chiral 3-amino-1-chloro-2-hydroxy-4-phenylbutanes were produced in excellent yields and diastereoselectivities (up to 99% yield, up to 99:1 dr). Both diastereomers of the desired products could be efficiently accessed by using the two enantiomers of the Rh(III) catalyst.

HIV infections are one of the world's greatest public health challenges, especially in the poor areas.[1] In 2018, over 37.9 million individuals worldwide were suffering from this disease, of which only 23.3 million had access to antiretroviral therapy, 1.7 million were newly infected and 0.77 million died.[2] HIV-1 protease inhibitors (HIV PIs) are considered to be one of the most promising chemotherapeutic agents against HIV infections.[3] To date, the approved HIV PIs by the US Food and Drug Administration (FDA) such as Atazanavir, Saquinavir, Ritonavir and Darunavir have been recommended by the World Health Organization as essential drugs for a basic health system.[4] Consequently, the development of highly efficient synthetic methods to access these HIV PIs is very important to reduce the cost and increase their usage in poverty-stricken areas. As can be seen from Figure 1, the HIV PIs have in common a chiral hydroxyethylamine moiety. To the best of our knowledge, the nucleophilic ring opening of the amino epoxides was the key step to construct this moiety and the amino epoxide intermediates (100's tons annually) can be prepared after base treatment of 3-amino-1-chloro-2-hydroxy-4-phenylbutanes **2** or **3** which in turn can be obtained by diastereoselective reduction of *N*-protected chloroketones **1**.

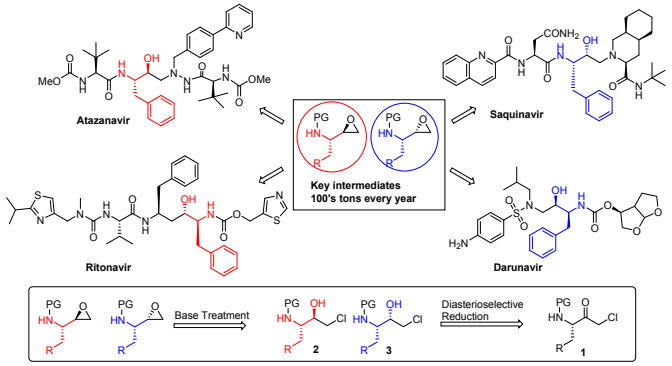
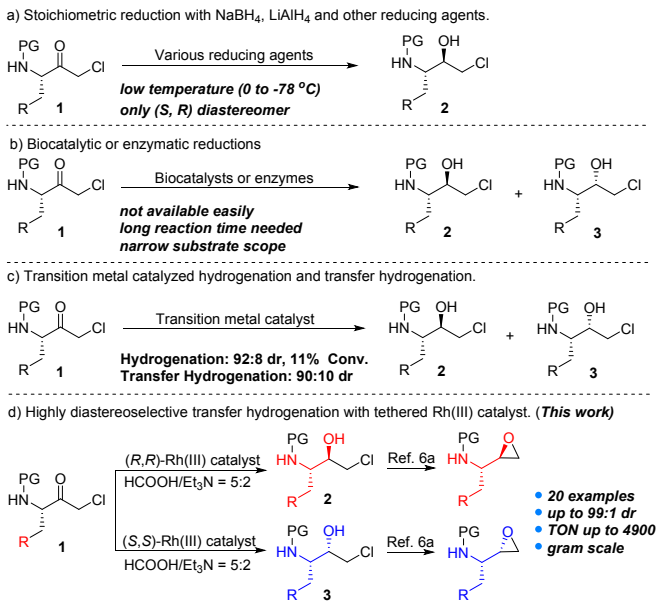


Figure 1. Selected privileged peptidomimetic HIV-1 inhibitors and their versatile synthetic intermediates.



Scheme 1. Previous work and this work.

During the last few decades, considerable efforts have been devoted to the diastereoselective reduction of chloroketones **1**.[5] $NaBH_4$ or $LiAlH_4$ reduction[6] and Meerwein–Ponndorf–Verley (MPV) reduction[7] of the corresponding ketones could only produce the diastereomer **2** and low temperature (0 to -78 °C) was needed to control the diastereoselectivity (Scheme 1a). Biocatalytic methods for the reduction of *N*-protected chloroketones **1** have also been reported.[8] However, these methods usually suffer from long reaction time, and the reaction outcome is highly substrate dependent. Besides, the preparation of the enzyme also requires elaborate and intricate methods, which limits their applicability and reproducibility (Scheme 1b). An asymmetric transfer hydrogenation of α-aminoalkyl α'-chloromethyl ketones **1** was reported[9] in 2004 using chiral Rh(III)/TsDPEN (*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) complex in a $HCOOH/NEt_3$ mixture delivering optically active alcohols with up to 90:10 dr and up to 1000 TON. A Rh(III)-catalyzed asymmetric hydrogenation of **1** was described[10] with 92: 8 dr, but with only 11% conversion (Scheme 1c). The combination of enzyme catalysis and asymmetric hydrogenation was also disclosed in 2003, albeit with low efficiency.[11] Although significant progress has

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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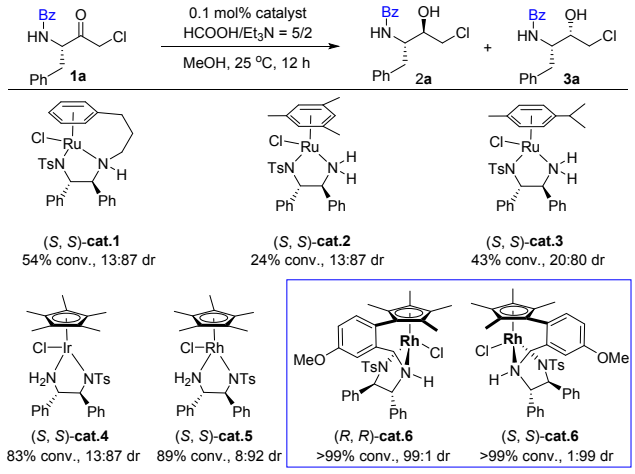
been achieved, the highly efficient and diastereoselective reduction of *α*-aminoalkyl *α'*-chloromethyl ketones **1** is still highly demanded.

Asymmetric transfer hydrogenation (ATH) has emerged as a new branch of enantioselective synthesis.[12] A variety of Ru, Rh, Ir catalysts in combination with the TsDPEN ligand was reported by Noyori, [13] Wills, [14] Xiao [15] and other groups.[16] These catalysts showed excellent catalytic performances in the ATH of ketones,[17] imines,[18] especially *α*-chloro ketones.[19] In particular, the tethered catalysts[20] developed by Wills and Ikariya, show greater activity and are more stable than the original non tethered catalysts. *Herein, we report a transfer hydrogenation strategy for the synthesis of chiral 3-amino-1-chloro-2-hydroxy-4-phenylbutane* ***2*** *with high efficiency (TON up to 4900) and high diastereoselectivity (up to 99:1 dr) (Scheme 1d).*



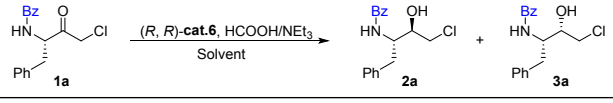
[a] Unless otherwise specified, the reactions were conducted with **1a** (0.2 mmol), catalyst (100 μL, 0.002 M in MeOH), HCOOH/Et_3N azeotropic mixture (40 μL) and MeOH (1.9 mL) at 25 °C, 12 h. The conversions were determined by ^1H NMR analysis and the dr values were determined by LCMS analysis.

Scheme 2. Evaluation of catalysts for the asymmetric transfer hydrogenation. [a]

We initially examined the transfer hydrogenation of **1a** using the commercially available TsDPEN-derived Ru, Rh and Ir complexes (0.1 mol %) in an azeotropic mixture of formic acid and triethylamine at 25 °C, and the results are depicted in Scheme 2. Catalysts **cat.1**, **cat.2**, **cat.3** and **cat.4** exhibited moderate activity and diastereoselectivity for this transformation. The use of (*S,S*)-**cat.5** afforded **2a** with 89% conversion and 8:92 dr. Pleasingly, the catalytic activity of tethered catalyst **cat.6** [21] outperformed that of the catalysts previously evaluated, both in conversion and diastereoselectivity. Reduction of **1a** with (*R,R*)-**cat.6** in azeotropic mixture of formic acid and triethylamine (S/C = 1000) in 0.1 M MeOH at 25 °C afforded **2a** with 99:1 dr value in complete conversion. The other diastereomer **3a** was obtained quantitatively using the enantiomer of the complex, (*S,S*)-**cat.6**, with 99:1 dr, demonstrating that the diastereoselectivity of the reduction was mainly controlled by the chirality of the ligand rather than the chirality of the adjacent stereogenic center.

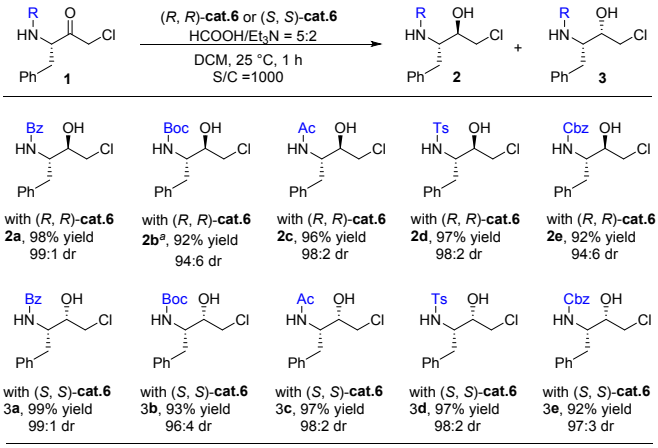
Encouraged by these promising results, we further examined the effect of the solvents and the ratio of formic acid and triethylamine on the reaction (Table 1). The solvents played an important role in this catalytic transformation. When toluene, THF, dioxane and ^{i}PrOH were used as solvent, >99% conversions were achieved after 3 h with 97:3 to 99:1 dr values (entries 2-4 and 6). The same conversions (>99%) were obtained in only 2 h in MeOH and 1 h in DCM with 99:1 dr value (entries 5 and 7). We next explored the influence of the catalyst loading. Using 0.02 mol% **cat.6**, 97% conversion was observed in DCM after 24 h with 99:1 dr, while only 55% conversion was achieved in MeOH for the same reaction time (entries 8-9). Additionally, the influence of the formic acid/triethylamine ratio was studied. Thus, the use of 3:2 and 1:1 mixtures as hydrogen donor source led to 96:4 dr and 98:2 dr respectively in full conversions in 4 h (entries 10-11).

Table 1. Optimization of reaction conditions for the Rh-catalyzed transfer hydrogenation of **1a**[a]



Entry	HCOOH/NEt_3	S/C[b]	Solvent	Time (h)	Conv. (%)[c]	dr[d]
1	5:2	1000	-	3	>99	98:2
2	5:2	1000	THF	3	>99	99:1
3	5:2	1000	^{i}PrOH	3	>99	99:1
4	5:2	1000	toluene	3	>99	99:1
5	5:2	1000	MeOH	2	>99	99:1
6	5:2	1000	dioxane	3	>99	97:3
7	5:2	1000	DCM	1	>99	99:1
8	5:2	5000	MeOH	24	55	99:1
9[e]	***5:2***	***5000***	***DCM***	***24***	***97***	***99:1***
10[e]	3:2	1000	DCM	4	>99	96:4
11[e]	1:1	1000	DCM	4	>99	98:2

[a] Reaction condition: 0.2 mmol of **1a** in 2.0 mL of solvent, catalyst (100 μL, 0.002 M in MeOH), HCOOH/Et_3N azeotropic mixture (40 μL), 25 °C. [b] The molar ratio of substrate and catalyst [c] Determined by ^1H NMR analysis. [d] Determined by LCMS analysis. [e] The catalyst (0.002 M in DCM).



[a] The reaction was carried out in MeOH.

Scheme 3. Evaluation of the effect of *N*-protecting groups.

With the optimal reaction condition in hand (entry 9), we evaluated the effect of *N*-protecting groups, and the results are summarized in Scheme 3. Chloromethyl ketones with various *N*-protecting groups could be reduced with (*S,S*)-**cat.6** and (*R,R*)-**cat.6**, delivering the desired chiral alcohols **2** and **3**. The yield and diastereoselectivity of the products were influenced by the configuration of catalyst **cat.6** as well

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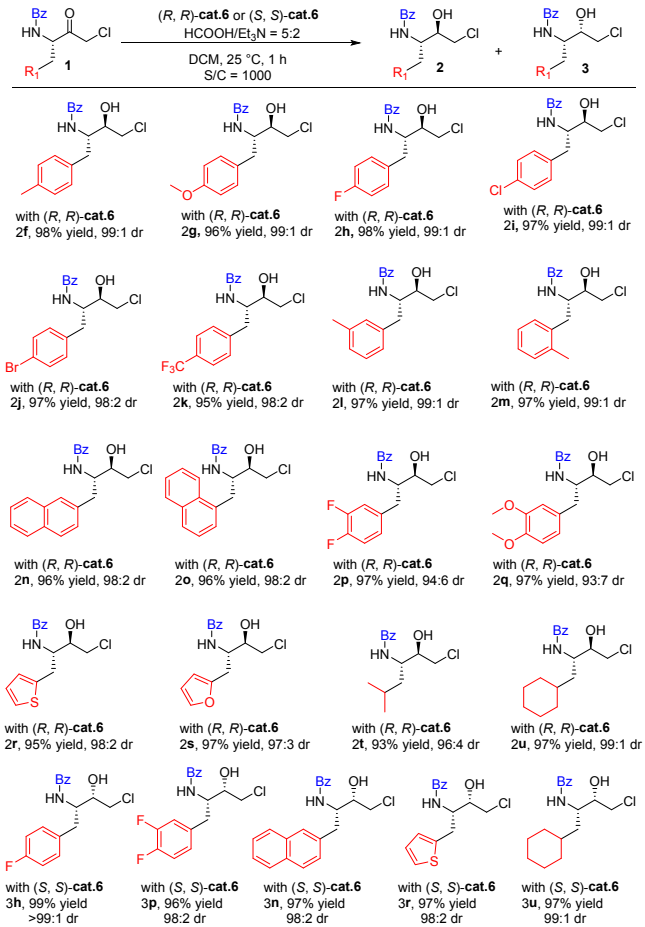
as by the *N*-protecting group. The reduction of **1b** and **1e** with (*S*,*S*)-**cat.6** gave the products with higher dr values than (*R*,*R*)-**cat.6**. The reaction of **1a** bearing a benzoyl protecting group gave the product with the highest dr value.



Scheme 4. Substrate scope of the Rh(III) catalyzed transfer hydrogenation.[a]

The substrate scope of this transformation was also evaluated, and the results are shown in Scheme 4. For substrates with electron-donating (Me and MeO) or electron-withdrawing groups (F, Cl, Br and CF_3) on the *para* position of the phenyl group, the reaction proceeded smoothly to provide the corresponding products in high yield and diastereoselectivity (**2f**-**2g** and **2h**-**2k**). The reaction also tolerated substrates with *meta*- or *ortho*-substitution on the phenyl group (**2l** and **2m**), and excellent yields and dr values were obtained. Slightly lower diastereoselectivity was achieved for substrates with naphthyl group or disubstituted phenyl group (**2n**-**2o** and **2p**-**2q**). Heterocyclic substituted compounds containing 2-thienyl or 2-furyl substituents were also tested furnishing **2r** and **2s** with excellent yield and dr value. When the aryl substituent was replaced by isopropyl or cyclohexyl groups, the corresponding products **2t** and **2u** were formed with 96:4 and 99:1 dr respectively. The other diastereomer **3** could be prepared in similar or higher diastereoselectivity (**3h**, **3p**, **3n**, **3r** and **3u**) by using (*S*,*S*)-**cat.6**.

To demonstrate the synthetic utility of this asymmetric transfer hydrogenation, four gram-scale transformations were conducted (Scheme 5). Under the standard reaction conditions, **1a** was converted to **2a** in 97% yield and 99:1 dr while **3a** was obtained in 93% yield and 99:1 dr using catalyst (*S*,*S*)-**cat.6**. Moreover, **2b** and **3b** were also obtained with >99:1 dr after recrystallization under the standard reaction conditions.

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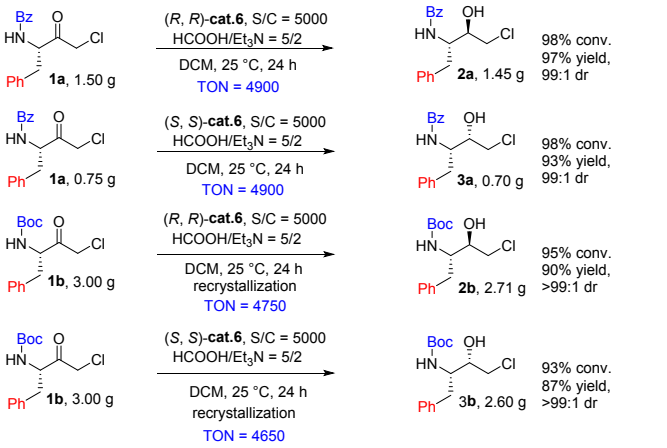

Scheme 5. Gram scale experiments.

In conclusion, we have developed an efficient Rh(III)-catalyzed diastereoselective transfer hydrogenation of *α*-aminoalkyl *α'*-chloromethyl ketones. As far as asymmetric transfer hydrogenation is concerned, this practical, operationally simple diastereoselective and functional-group-tolerant method allows to efficiently access both diastereomers of the corresponding alcohols at low catalyst loading, in high yield and diastereoselectivity (up to 99% yield, up to 99:1 dr, up to 4900 TON). Direct access to a variety of chloro hydroxylamines was achieved using the disclosed method providing an efficient and concise route to 1-chloro-2-hydroxy-4-phenylbutanes, which are key intermediates of HIV protease inhibitors.

Acknowlegment

X. Zhang is indebted to Shenzhen Nobel Prize Scientists Laboratory Project (C17213101), Southern University of Science and Technology (start-up fund), Shenzhen Science and Technology Innovation Committee (Nos. KQTD20150717103157174 and JSGG20170821140353405), National Natural Science Foundation of China (Nos. 21432007 and 21672094) and SZDRC Discipline Construction Program for financial support.

Conflicts of interest

The authors declare no competing financial interests.

Notes and references

1. (a) A. G. Tomasselli and R. L. Heinrikson, *Biochim. Biophys. Acta, Protein Struct. Mol. Enzymol.*, 2000, **1477**, 189-214; (b) M. S. Cohen, N. Hellmann, J. A. Levy, K. DeCock and J. Lange, *J. Clin. Invest.*, 2008, **118**, 1244-1254; (c) K. A. Sepkowitz, *N. Engl. J. Med.*, 2001, **344**, 1764-1772.

2. M. Sidibé, *World AIDS Day Report*, 2019, **https://www.unaids.org/en/re-sources/fact-sheet**.

3. (a) T. Cihlar and M. Fordyce, *Curr. Opin. Virol.*, 2016, **18**, 50-56; (b) H. F. Gunthard, J. A. Aberg, J. J. Eron, J. F. Hoy, A. Telenti, C. A. Benson, D. M. Burger, P. Cahn, J. E. Gallant, M. J. Glesby, P. Reiss, M. S. Saag, D. L. Thomas, D. M. Jacobsen and P. A. Volberding, *J.*

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Am. Med. Assoc., 2014, **312**, 410-425; (c) P. Zhan, C. Pannecouque, E. De Clercq and X. Liu, *J. Med. Chem.*, 2016, **59**, 2849-2878.

4. (a) A. Wlodawer and J. Vondrasek, *Annu. Rev. Biophys. Biomol. Struct.*, 1998, **27**, 249-284; (b) J. C. Craig, I. B. Duncan, D. Hockley, C. Grief, N. A. Roberts and J. S. Mills, *Antiviral Res.*, 1991, **16**, 295-305; (c) J. Y. Feng, F. Myrick, B. Selmi, J. Deval, B. Canard and K. Borroto-Esoda, *Antiviral Res.*, 2005, **66**, 153-158; (d) K. F. Croom, S. Dhillon and S. J. Keam, *Drugs*, 2009, **69**, 1107-1140; (e) A. K. Ghosh, H. L. Osswald and G. Prato, *J. Med. Chem.*, 2016, **59**, 5172-5208.

5. (a) K. Izawa and T. Onishi, *Chem. Rev.*, 2006, **106**, 2811-2827; (b) A. M. S. M, S. Mandlekar, S. Desikan, T. Ramar, L. Subramani, M. Annadurai, S. D. Desai, S. Sinha, S. M. Jenkins, M. R. Krystal, M. Subramanian, S. Sridhar, S. Padmanabhan, P. Bhutani, R. Arla, S. Singh, J. Sinha, M. Thakur, J. F. Kadow and N. A. Meanwell, *J. Med. Chem.*, 2019, **62**, 3553-3574; (c) J. Barluenga, B. Baragana and J. M. Concellon, *J. Org. Chem.*, 1995, **60**, 6696-6699; (d) B. M. Kim, S. J. Bae, S. M. So, H. T. Yoo, S. K. Chang, J. H. Lee and J. Kang, *Org. Lett.*, 2001, **3**, 2349-2351; (e) A. J. Blacker, M. Roy, S. Hariharan, C. Headley, A. Upare, A. Jagtap, K. Wankhede, S. K. Mishra, D. Dube, S. Bhise, S. Vishwasrao and N. Kadam, *Org. Pro. Res. Dev.*, 2011, **15**, 331-338.

6. (a) C. L. Liotta, P. Pollet, K. Kitagawa, W. Dubay and J. Stringer, WO2011060302A1, 2011; (b) T. Torii, T. Hamada, T. Onishi, K. Izawa, T. Ikariya and R. Noyori, WO2002051781A1, 2002; (c) J. Yin, X. Ju, B. Li and J. Tao, CN103468757A, 2013; (d) A. Albeck and G. I. Estreicher, *Tetrahedron*, 1997, **53**, 5325-5338.

7. (a) A. K. Dilger, V. Gopalsamuthiram and S. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 16273-16277; (b) J. Yin, M. A. Huffman, K. M. Conrad and J. D. Armstrong, 3rd, *J. Org. Chem.*, 2006, **71**, 840-843; (c) K. Flack, K. Kitagawa, P. Pollet, C. A. Eckert, K. Richman, J. Stringer, W. Dubay and C. L. Liotta, *Org. Pro. Res. Dev.*, 2012, **16**, 1301-1306.

8. (a) K. Goldberg, K. Schroer, S. Luetz and A. Liese, *Appl. Microbiol. Biotechnol.*, 2007, **76**, 249-255; (b) K. Goldberg, K. Schroer, S. Lutz and A. Liese, *Appl. Microbiol. Biotechnol.*, 2007, **76**, 249-255; (c) A. S. de Miranda, R. C. Simon, B. Grischek, G. C. de Paula, B. A. C. Horta, L. S. M. de Miranda, W. Kroutil, C. O. Kappe and R. O. M. A. de Souza, *ChemCatChem*, 2015, **7**, 984-992; (d) R. N. Patel, A. Banerjee, C. G. McNamee, D. B. Brzozowski and L. J. Szarka, *Tetrahedron: Asymmetry*, 1997, **8**, 2547-2552.

9. T. Hamada, T. Torii, T. Onishi, K. Izawa and T. Ikariya, *J. Org. Chem.*, 2004, **69**, 7391-7394.

10. M. W. Pennington and A. Hodgson, WO2006016116A1, 2006.

11. I. N. Houpis, R. Liu, L. Liu, Y. Wang, N. Dong, X. Zhao, Y. Zhang, T. Xiao, Y. Wang, D. Depre, U. Nettekoven, M. Vogel, R. Wilson and S. Collier, *Adv. Synth. Catal.*, 2013, **355**, 1829-1839.

12. (a) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97-102; (b) W. Baratta, G. Chelucci, S. Gladiali, K. Siega, M. Toniutti, M. Zanette, E. Zangrando and P. Rigo, *Ang. Chem., Int. Ed.*, 2005, **44**, 6214-6219; (c) C. Sui-Seng, F. Freutel, A. J. Lough and R. H. Morris, *Ang. Chem., Int. Ed.*, 2008, **47**, 940-943; (d) Z. L. Xia, C. Zheng, S. G. Wang and S. L. You, *Ang. Chem., Int. Ed.*, 2018, **57**, 2653-2656; (e) Q. Zhou, W. Meng, J. Yang and H. Du, *Ang. Chem., Int. Ed.*, 2018, **57**, 12111-12115; (f) D. Wang and D. Astruc, *Chem. Rev.*, 2015, **115**, 6621-6686; (g) G. Zassinovich, G. Mestroni and S. Gladiali, *Chem. Rev.*, 1992, **92**, 1051-1069; (h) C. Zheng and S. L. You, *Chem. Soc. Rev.*, 2012, **41**, 2498-2518; (i) J. Muzart, *Eur. J. Org. Chem.*, 2015, **2015**, 5693-5707; (j) A. Mikhailine, A. J. Lough and R. H. Morris, *J. Am. Chem. Soc.*, 2009, **131**, 1394-1395; (k) A. A. Mikhailine, M. I. Maishan, A. J. Lough and R. H. Morris, *J. Am. Chem. Soc.*, 2012, **134**, 12266-12280; (l) P. Roszkowski and Z. Czarnocki, *Mini-Rev. Org. Chem.*, 2007, **4**, 190-200.

13. (a) M. Yamakawa, I. Yamada and R. Noyori, *Angew. Chem., Int. Ed.*, 2001, **40**, 2818-2821; (b) K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738-8739; (c) T. Ohkuma, N. Utsumi, K. Tsutsumi, K. Murata, C. Sandoval and R. Noyori, *J. Am. Chem. Soc.*, 2006, **128**, 8724-8725.

14. (a) R. C. Knighton, V. K. Vyas, L. H. Mailey, B. M. Bhanage and M. Wills, *J. Organomet. Chem.*, 2018, **875**, 72-79; (b) J. Barrios-Rivera, Y. Xu and M. Wills, *Org. Lett.*, 2019, **21**, 7223-7227; (c) S. Forshaw, A. J. Matthews, T. J. Brown, L. J. Diorazio, L. Williams and M. Wills, *Org. Lett.*, 2017, **19**, 2789-2792; (d) J. E. D. Martins, G. J. Clarkson and M. Wills, *Org. Lett.*, 2009, **11**, 847-850; (e) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson and M. Wills, *Org. Lett.*, 2005, **7**, 5489-5491; (f) R. Soni, J.-M. Collinson, G. C. Clarkson and M. Wills, *Org. Lett.*, 2011, **13**, 4304-4307.

15. (a) Y. Pan, Z. Luo, X. Xu, H. Zhao, J. Han, L. Xu, Q. Fan and J. Xiao, *Adv. Synth. Catal.*, 2019, **361**, 3800-3806; (b) W. Tang, S. Johnston, J. A. Iggo, N. G. Berry, M. Phelan, L. Lian, J. Bacsa and J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 1668-1672; (c) C. Wang, C. Li, X. Wu, A. Pettman and J. Xiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 6524-6528; (d) C. Wang, A. Pettman, J. Basca and J. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 7548-7552; (e) X. Wu, X. Li, F. King and J. Xiao, *Angew. Chem., Int. Ed.*, 2005, **44**, 3407-3411.

16. (a) M. T. Corbett and J. S. Johnson, *J. Am. Chem. Soc.*, 2013, **135**, 594-597; (b) S. K. Murphy and V. M. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 5553-5556; (c) Z. Q. Rong, Y. Zhang, R. H. Chua, H. J. Pan and Y. Zhao, *J. Am. Chem. Soc.*, 2015, **137**, 4944-4947; (d) K. M. Steward, M. T. Corbett, C. G. Goodman and J. S. Johnson, *J. Am. Chem. Soc.*, 2012, **134**, 20197-20206; (e) T. Touge, H. Nara, M. Fujiwhara, Y. Kayaki and T. Ikariya, *J. Am. Chem. Soc.*, 2016, **138**, 10084-10087; (f) T. Cheng, Q. Ye, Q. Zhao and G. Liu, *Org. Lett.*, 2015, **17**, 4972-4975.

17. (a) P. O. Lagaditis, A. J. Lough and R. H. Morris, *J. Am. Chem. Soc.*, 2011, **133**, 9662-9665; (b) B. He, P. Phansavath and V. Ratovelomanana-Vidal, *Org. Lett.*, 2019, **21**, 3276-3280; (c) C. S. G. Seo and R. H. Morris, *Organometallics*, 2019, **38**, 47-65.

18. (a) S. Li, G. Li, W. Meng and H. Du, *J Am Chem Soc*, 2016, **138**, 12956-12962; (b) M. Wu, T. Cheng, M. Ji and G. Liu, *J. Org. Chem.*, 2015, **80**, 3708-3713; (c) A. A. Mikhailine, M. I. Maishan and R. H. Morris, *Org. Lett.*, 2012, **14**, 4638-4641; (d) C. Xu, Y. Feng, F. Li, J. Han, Y.-M. He and Q.-H. Fan, *Organometallics*, 2019, **38**, 3979-3990.

19. (a) A. Matsunami, M. Ikeda, H. Nakamura, M. Yoshida, S. Kuwata and Y. Kayaki, *Org Lett*, 2018, **20**, 5213-5218; (b) L. S. Zheng, P. Phansavath and V. Ratovelomanana-Vidal, *Org Lett*, 2018, **20**, 5107-5111.

20. (a) J. Hannedouche, G. J. Clarkson and M. Wills, *J. Am. Chem. Soc.*, 2004, **126**, 986-987; (b) A. M. Hayes, D. J. Morris, G. J. Clarkson and M. Wills, *J. Am. Chem. Soc.*, 2005, **127**, 7318-7319; (c) T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki and T. Ikariya, *J. Am. Chem. Soc.*, 2011, **133**, 14960-14963; (d) T. Touge, K. Sakaguchi, N. Tamaki, H. Nara, T. Yokozawa, K. Matsumura and Y. Kayaki, *J. Am. Chem. Soc.*, 2019, **141**, 16354-16361.

21. P.-G. Echeverria, C. Ferard, P. Phansavath and V. Ratovelomanana-Vidal, *Catal. Commun.*, 2015, **62**, 95-99.

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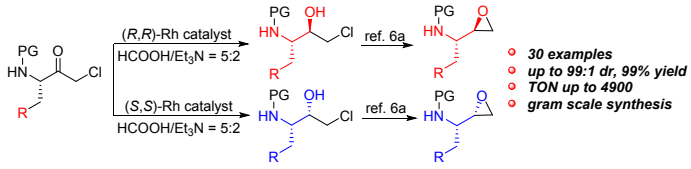
Rh(III)-Catalyzed Diastereoselective Transfer Hydrogenation: an Efficient Entry to Key Intermediates of HIV Protease Inhibitors



A highly efficient diastereoselective transfer hydrogenation of α-aminoalkyl α'-chloromethyl ketones catalyzed by a tethered rhodium complex was developed and successfully utilized in the synthesis of the key intermediates of HIV protease inhibitors. With the current Rh(III) catalyst system, a series of chiral 3-amino-1-chloro-2-hydroxy-4-phenylbutanes were produced in excellent yields and diastereoselectivities (up to 99% yield, up to 99:1 dr). Both diastereomers of the desired products could be efficiently accessed by using the two enantiomers of the Rh(III) catalyst.

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DOI: 10.1039/D0CC00990D

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