Synthesis of Diols by Site-Selective Oxidation of Alcohols



LS 2017/06/03 Hiroki Fujisawa (D3)

Introduction of OH Group



Table of Contents

- 1. Synthesis of 1,4-diol
 - Radical approach (Chiba's study)



- 2. Synthesis of 1,3-diol
 - Radical approach (Baran's study)
 - Ir-catalyzed silylation approach (Hartwig's study)

- 3. Synthesis of 1,2-diol
 - Pd-catalyzed oxidation (Dong's study)

C-H Activation by 1,5-Hydrogen Shift



Copper Catalyzed C-H Activation

Copper catalyzed C-H oxidation under O₂ atmosphere



Zhang, L.; Ang, G. Y.; Chiba, S. Org. Lett. 2011, 13, 1622.

Copper catalyzed C-H chlorination



1,4-Diol Synthesis under O₂ Atmosphere



Too, P. C.; Tnay, Y. L.; Chiba, S. Beilstein. J. Org. Chem. 2013, 9, 1217.

Proposed Mechanism of Cu-Catalyzed Oxidation



Substrate Scope (Oxidation of CH₂ by tert-OOH)





Too, P. C.; Tnay, Y. L.; Chiba, S. Beilstein. J. Org. Chem. 2013, 9, 1217.

Substrate Scope (Oxidation of CH by tert-OOH)



Too, P. C.; Tnay, Y. L.; Chiba, S. Beilstein. J. Org. Chem. 2013, 9, 1217.

Substrate Scope (Oxidation of CH₂ by sec-OOH)



1,3-Diol Synthesis by C-H activation



Today's contents

1. Radical approach (Baran's group)

2. Ir-catalyzed silylation approach (Hartwig's group)

1,3-Diol Synthesis by Radical Reaction



Chen, K.; Richter, J. M.; Baran, P. S. J. Am. Chem. Soc. 2008, 130, 7247.

Optimization of Carbamate Unit





stability of N-radical

yield of alkyl bromide reactivity of N-radical

Chen, K.; Richter, J. M.; Baran, P. S. J. Am. Chem. Soc. 2008, 130, 7247.

Explanation for Stereoselectivity (My Opinion)



(dr = not mentioned)

Regioselectivity



C-H Silylation Developed by Hartwig's Group



Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70.

Proposed Mechanism of Silyletherification



Proposed Mechanism of C-H Silylation



Methyl Selective Silylation

[lr(cod)OMe]₂ (1 mol%) 3,4,7,8-Me₄ phen (1 mol%) Et₂ norbornene -SiEt₂ THF, 80 °C Ph Ph [lr(cod)OMe]₂ (1 mol%) 3,4,7,8-Me₄ phen (1 mol%) norbornene Et₂ THF, 80 °C -SiEt₂ н Ph Pł $K_{\text{methyl}}/K_{\text{methylene}} = 49 \pm 2$ $[lr(cod)OMe]_2$ (1 mol%) 3,4,7,8-Me₄ phen (1 mol%) iEt₂H -SiEt₂ Et₂Si norbornene THF, 80 °C 94% $(A : B = 41 \pm 2 : 1)$ Α В

Silylation Occurred at Less Hindered Position





Li, B.; Driess, M.; Hartwig, J. F. J. Am. Chem. Soc. 2014, 136, 6586.

A Limitation in Silylation



Short Summary (1,3-Diol Synthesis)



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1. Synthesis of 1,4-diol

- Radical approach (Chiba's study)

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due to the inductive effect of OR group

Oxime Directed C-H Oxidation



Desai, L. V.; Hull, K. L.; Sandord, M. S. J. Am. Chem. Soc. 2004, 126, 9542.

Reaction design



Ren, Z.; Mo, F.; Dong, G. J. Am. Chem. Soc. 2012, 134, 16991.

1,2-Diol Synthesis by Oxime Directed C-H Oxidation



Ren, Z.; Mo, F.; Don, G. J. Am. Chem. Soc. 2012, 134, 16991.

Proposed Mechanism of Oxime Directed C-H Oxidation



Substrate Scope and Selective Deprotection



Summary



APPENDIX

Mechanism of Cu-Catalyzed Aerobic Oxidation



Mechanism of Cu-Catalyzed Chlorination



Details in Catalytic Cycle of Silylation



Energy Profile in Silylation



KIE Study of Silylation



Optimization for C-H Silylation



entry	R ¹	R ²	ligand	conv (%)	yield (%)
1	<i>n-</i> Pr	Et	L1	83	76
2	<i>n-</i> Pr	Et	L2	62	55
3	<i>n-</i> Pr	Et	L3	88	82
4	<i>n-</i> Pr	Et	L4	100	94
5	н	Et	L4	92	< 10
6	<i>n-</i> Pr	Ме	L4	100	89
7	<i>n-</i> Pr	<i>i</i> -Pr	L4	12	< 10
^{tBu}	L1	R³ R⁴-		R^{3} $R^{3} = 0$ $R^{4} R^{3} = 0$ $R^{3} = 0$	CI, R ⁴ = H, L2 R ⁴ = H, L3 R ⁴ = Me, L4

Introduction of Oxime Directing Group



KIE Study in Oxime Directed C-H Oxidation

