Published in final edited form as:

Chemistry. 2017 February 21; 23(11): 2557–2559. doi:10.1002/chem.201606046.

Enantioselective Synthesis of Oxetanes Bearing All-Carbon Quaternary Stereocenters *via* Iridium Catalyzed Alcohol-Vinyl Epoxide C-C Coupling**

Dr. Yi-An Guo, Dr. Wonchul Lee, and Prof. Michael J. Krische*

University of Texas at Austin, Department of Chemistry, 1 University Station – A5300, Austin, TX 78712-1167 (USA)

Taming the Oxetane

Oxetanes bearing all-carbon quaternary stereocenters are readily prepared through the iridium catalyzed *anti*-diastereo- and enantioselective C-C coupling of primary alcohols and isoprene oxide. Based on this methodology, an oxetane containing analogue of haloperidol was prepared. A related azetidine formation also is described.

Graphical abstract

Keywords

Iridium; Enantioselective; Oxetane; Transfer Hydrogenation; Quaternary Center

Introduction

Oxetanes are useful building blocks in chemical synthesis^[1] and are finding increasing use in medicinal chemistry due to their metabolic stability and capacity to serve as structural and functional equivalents to carbonyl and *gem*-dimethyl moieties.^[2] Despite significant advances in the development of methods for oxetane synthesis,^[3] diastereo- and enantioselective methods for the construction of oxetanes bearing all-carbon quaternary stereocenters are unknown beyond the context of spirocyclic systems.^[3b] As part of a broad program aimed at the development of C-C bond forming hydrogenations and transfer hydrogenations,^[4] we recently reported the byproduct-free coupling of primary alcohols

** Acknowledgment is made to the Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) for partial financial support.

* mkrische@mail.utexas.edu.

with isoprene oxide to form products of *tert*-(hydroxy)-prenylation – a process that occurs with exceptional control of *anti*-diastereo- and enantioselectivity.^[5] It was posited that the neopentyl glycols obtained in these couplings might serve as precursors to 2,3-trisubstituted oxetanes bearing all-carbon quaternary stereocenters. For optimal impact on medicinal chemistry, these synthetic procedures should be compatible with diverse *N*-heteroaromatic substructures, however, our initial exploration of the iridium catalyzed *tert*-(hydroxy)-prenylation did not encompass this aspect of chemoselectivity. Here, in fulfilment of these objectives, we now report the first diastereo- and enantioselective synthesis of 2,3-trisubstituted oxetanes bearing all-carbon quaternary stereocenters *via* isoprene oxide mediated alcohol C-H *tert*-(hydroxy)-prenylation (Figure 1).

Results and Discussion

In an initial experiment aimed at probing compatibility with Lewis basic *N*-heterocycles, 2-chloro-5-hydroxymethylpyridine **1a** was exposed to commercially available isoprene oxide (300 mol%) and potassium phosphate (5 mol%) in the presence of the chromatographically purified π -allyliridium *C,O*-benzoate complex modified by (*S*)-Tol-BINAP in THF solvent at 60 °C (Figure 1). To our delight, the product of *tert*-(hydroxy)-prenylation **2a** was formed in 91% yield with 40:1 *anti*-diastereoselectivity and 93% enantiomeric excess. Encouraged by these results, diverse aromatic *N*-bearing heterocycles **1a–1g** were evaluated under these conditions (Table 1). Notwithstanding minor variation in reaction temperature (45 or 60 °C) and loading of isoprene oxide (300–400 mol%), the products of *tert*-(hydroxy)-prenylation **2a–2g** were formed with comparable levels of *anti*-diastereo- and enantioselectivity. Here, a substituent adjacent to nitrogen is required to enforce catalytic turnover. Fluorinated benzylic alcohols **1h** and **1i**, allylic alcohol **1j** and the *N*-Boc-protected aminopropanol **1k** also participated in highly diastereo- and enantioselective *tert*-(hydroxy)-prenylation to form adducts **2h–2k**, respectively (Table 1). The stereochemical assignments of adducts **2a–2k** were made in analogy to that determined for adduct **2f**, which was established by single crystal x-ray diffraction analysis.

Conversion of the diol-containing adducts **2a–2k** to the corresponding oxetanes **3a–3k** was accomplished through a 2-step protocol.^[6] First, highly chemoselective tosylation of the primary alcohol moiety was achieved through exposure of adducts **2a–2k** to *p*-toluenesulfonyl chloride in pyridine solvent at 55 °C.^[6a] The resulting *mono*-tosylates were dissolved in THF solvent at 0 °C and treated with butyl lithium to promote S_N2 cyclization, affording the 2,3-trisubstituted oxetanes **3a–3k**.^[6b] Attempted *mono*-tosylation of diol **2c** under these conditions resulted in indolizidinium formation. In this case, a one-pot procedure for successive mesylation-sodium hydride-mediated cyclization^[7] enabled direct access to the oxetane **3c**. The stereochemical assignments of oxetanes **3a–3k** were made in analogy to that determined for **3d**, which was established by single crystal x-ray diffraction analysis.

To illustrate the utility of this asymmetric protocol for oxetane formation, the *p*-fluorophenyl substituted oxetane **1i** was converted to an analogue of the landmark antipsychotic agent haloperidol, which is among the *WHO Model List of Essential Medicines* (Scheme 1).^[8] The enhanced basicity of the oxetane oxygen is meant to mimic the carbonyl oxygen of

haloperidol.^[2] Additionally, the oxetane provides a conformational constraint.^[2] Hydroboration of oxetane **3i** using 9-BBN (9-borabicyclo[3.3.1]nonane) delivered the primary alcohol **4** in 80% yield as a single regioisomer. Interestingly, attempted use of borane itself led to significant quantities of the corresponding Markovnikov hydration product, presumably due to the directing effect of the relatively Lewis basic oxetane oxygen.^[9] Conversion of **4** to the mesylate followed by treatment with 4-chlorophenyl-4-hydroxy-piperidine **5** provides the haloperidol analogue **6**. (Scheme 1).

To further illustrate how oxetanes **3a–3k** may serve as building blocks in chemical synthesis,^[11] oxetane **3b** was converted to the enantiomerically enriched tetrasubstituted cyclopropane **7** in 78% yield through exposure to phenyl magnesium bromide in the presence of a nickel(II) catalyst (Scheme 2, eq. 1). Unlike related nickel catalyzed processes,^[11] stereospecific C-O oxidative addition is followed by olefin insertion and C-C reductive elimination to form cyclopropane **7** a single diastereomer. Beyond the synthesis of oxetanes, the present methodology also provides facile access to enantiomerically enriched trisubstituted azetidines. For example, conversion of diol **2i** to the *bis*-mesylate^[12] followed by exposure to neat benzylamine^[12] provides the azetidine **8** (Scheme 2, eq. 2).

Conclusion

In summary, the first asymmetric synthesis of oxetanes bearing all-carbon quaternary stereocenters (beyond spirocyclic systems) is enabled through the *anti*-diastereo- and enantioselective iridium catalyzed C-C coupling of primary alcohols and isoprene oxide. The prospect of deploying this methodology in the context of medicinal chemistry is established by the preparation of oxetane **6**, an analogue of the antipsychotic agent haloperidol. Finally, as demonstrated by the preparation of cyclopropane **7** and azetidine **8**, the present chemistry offers a novel means of accessing other enantiomerically enriched small ring compounds bearing all-carbon quaternary stereocenters – an aspect that will serve as the basis for future research.

Experimental Section

Representative procedure for iridium catalyzed alcohol C-H *tert*-(hydroxy)-prenylation

(1*R*, 2*R*)-1-(6-methoxypyridin-3-yl)-2-methyl-2-vinylpropane-1, 3-diol (2b)—An oven-dried pressure tube equipped with a magnetic stir bar was charged with K₃PO₄ (2.2 mg, 0.01 mmol, 5 mol%), (*S*)-Ir-Tol-BINAP (11.0 mg, 0.01 mmol, 5 mol%) and 2-methoxy-5-hydroxymethylpyridine **1b** (27.8 mg, 0.2 mmol, 100 mol%). Under an atmosphere of argon, anhydrous THF (0.4 mL, 0.5 M) and isoprene monoxide (59 μ L, 0.6 mmol, 300 mol%) were sequentially added via syringe. The pressure tube was sealed and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature and was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO₂, hexanes:ethyl acetate, 1:1) to furnish the title compound as a yellow oil (42 mg, 0.19 mmol, *anti:syn* > 20:1, 90% ee) in 94% yield.

Representative procedure for diol mono-tosylation

(R)-2-((R)-hydroxy(6-methoxypyridin-3-yl)methyl)-2-methylbut-3-en-1-yl 4-methyl-benzenesulfonate (3b')—An oven-dried vial equipped with a magnetic stir bar was charged with diol **2b** (22.3 mg, 0.1 mmol, 100 mol%) and tosyl chloride (26.7 mg, 0.14 mmol, 140 mol%). Under an argon atmosphere, pyridine (0.2 mL, 0.5 M) was added via syringe. The reaction mixture was stirred at 55 °C for 9 h. The reaction was allowed to cool to ambient temperature and aqueous phosphoric acid (10 mL, 0.5 M) was added. The aqueous layer was extracted with ethyl acetate (30 mL × 2). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO₂, hexanes: ethyl acetate = 3:1) to furnish the title compound as a yellow oil (34.0 mg, 0.09 mmol) in 90% yield.

Representative procedure for oxetane formation

2-methoxy-5-((2R, 3S)-3-methyl-3-vinylloxetan-2-yl)pyridine (3b)—A flame-dried vial equipped with a magnetic stir bar was charged with the mono-tosylate derived from **2b** (30.0 mg, 0.08 mmol, 100 mol%). Under an atmosphere of argon, anhydrous THF (0.8 mL, 0.1 M) was added via syringe. The reaction mixture was cooled to 0 °C before *n*-butyl lithium (35 µL, 0.088 mmol, 110 mol%, 2.5 M in hexanes) was added. The reaction was stirred at 0 °C for 30 min and then warmed to ambient temperature. After further stirring for 2.5 h, saturated aqueous ammonium chloride (10 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl ether (30 mL × 2). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO₂, pentane: ethyl ether = 10:1) to furnish the title compound as a yellow oil (13.1 mg, 0.06 mmol) in 79% yield.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. For recent reviews on the use of oxetanes as building blocks in chemical synthesis, see: Mack DJ, Njardarson JT. ACS Catal. 2013; 3:272–286. Njardarson JT. Synlett. 2013:787–803. Wang Z, Chen Z, Sun J. Org Biomol Chem. 2014; 12:6028–6032. [PubMed: 24968137] Malapit CA, Howell AR. J Org Chem. 2015; 80:8489–8495. [PubMed: 26225624]
2. For recent reviews on the use of oxetanes in medicinal chemistry, see: Burkhard JA, Wuitschik G, Rogers-Evans M, Müller K, Carreira EM. Angew Chem. 2010; 122:9236–9251. Angew Chem Int Ed. 2010; 49:9052–9067. StJean DJ Jr, Fotsch C. J Med Chem. 2012; 55:6002–6020. [PubMed: 22533875] Bull JA, Croft RA, Davis OA, Doran R, Morgan KF. Chem Rev. 2016; 116:12150–12233. [PubMed: 27631342]
3. For recent reviews on the synthesis of oxetanes, see: D'Auria M, Racioppi R. Molecules. 2013; 18:11384–11428. [PubMed: 24043139] Carreira EM, Fessard TC. Chem Rev. 2014; 114:8257–8322. [PubMed: 25003801] Davis OA, Bull JA. Synlett. 2015:1283–1288.
4. For recent reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: Hassan A, Krische MJ. Org Proc Res Devel. 2011; 15:1236–1242. Ketcham JM, Shin I, Montgomery TP, Krische MJ. Angew Chem. 2014; 126:9294–9302. Angew Chem Int Ed. 2014; 53:9142–9150. Feng J, Kasun ZA, Krische MJ. J Am Chem Soc. 2016; 138:5467–5478. [PubMed: 27113543]
5. Feng J, Garza VJ, Krische MJ. J Am Chem Soc. 2014; 136:8911–8914. [PubMed: 24915473]

6. a) Kurokawa N, Ohfuné Y. *J Am Chem Soc.* 1986; 108:6041–6043. [PubMed: 22175372] b) Ito K, Fukuda T, Katsuki T. *Heterocycles.* 1997; 46:401–411.
7. Isaacs RCA, Di Grandi MJ, Danishefsky SJ. *J Org Chem.* 1993; 58:3938–3941.
8. a) Settle EC Jr, Ayd FJ Jr. *J Clin Psych.* 1983; 44:440–448. b) Granger B. *Encephale.* 1999; 25:59–66. [PubMed: 10205735] c) Lopez-Munoz F, Alamo C. *Brain Res Bull.* 2009; 79:130–141. [PubMed: 19186209]
9. a) Wilt JW, Narutis VP. *J Org Chem.* 1979; 44:4899–4905. b) Coppi DI, Salomone A, Perna FM, Capriati V. *Angew Chem.* 2012; 124:7650–7654. *Angew Chem Int Ed.* 2012; 51:7532–7536.
10. Szabo M, Klein Herenbrink C, Christopoulos A, Lane JR, Capuano B. *J Med Chem.* 2014; 57:4924–4939. [PubMed: 24827597]
11. a) Tollefson EJ, Dawson DD, Osborne CA, Jarvo ER. *J Am Chem Soc.* 2014; 136:14951–14958. [PubMed: 25308512] b) Tollefson EJ, Hanna LE, Jarvo ER. *Acc Chem Res.* 2015; 48:2344–2353. [PubMed: 26197033]
12. Banwell MG, Edwards AJ, Harfoot GJ, Jolliffe KA. *Tetrahedron.* 2004; 60:535–547.
13. Maity JK, Ghosh R, Drew MG, Achari B, Mandal SB. *J Org Chem.* 2008; 73:4305–4308. [PubMed: 18433176]

Figure 1. Enantioselective synthesis of oxetanes bearing all-carbon quaternary stereocenters *via* iridium catalysis.

Scheme 1.

Synthesis of an oxetane-bearing analogue of the antipsychotic agent haloperidol.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Conversion of oxetane **3b** to cyclopropane **7** and conversion of diol **3i** to azetidine **8**.^a

Chemistry. Author manuscript; available in PMC 2018 February 21.

Table 1

Iridium catalyzed coupling of isoprene oxide with alcohols **1a–1k** to form neopentyl glycols **2a–2k** and conversion to 2,3-trisubstituted oxetanes **3a–3k**.^a

1a , R = Cl 1b , R = OMe	2a , R = Cl 91% Yield, 40:1 dr, 93% ee 2b , R = OMe 94% Yield, 99:1 dr, 90% ee	3a , R = Cl 91% Yield (1), 82% Yield (2) ^b 3b , R = OMe 90% Yield (1), 79% Yield (2)
1c	2c 85% Yield, 30:1 dr, 99% ee	3c 55% Yield ^c
1d	2d 78% Yield, 99:1 dr, 96% ee	3d (X-Ray) 80% Yield (1), 80% Yield (2)
1e	2e 80% Yield, 80:1 dr, 92% ee ^{b,d}	3e 83% Yield (1), 72% Yield (2)
1f	2f (X-Ray) 89% Yield, 99:1 dr, 95% ee	3f 83% Yield (1), 89% Yield (2)
1g	2g 81% Yield, 30:1 dr, 99% ee	3g 82% Yield (1), 77% Yield (2) ^b
1h , R ¹ = CF ₃ , R ² = H 1i , R ¹ = H, R ² = F	2h , R ¹ = CF ₃ , R ² = H 2i , R ¹ = H, R ² = F 82% Yield, 70:1 dr, 94% ee 89% Yield, 30:1 dr, 94% ee	3h , R ¹ = CF ₃ , R ² = H 3i , R ¹ = H, R ² = F 91% Yield (1), 88% Yield (2) 89% Yield (1), 69% Yield (2) ^b
1j	2j 79% Yield, 99:1 dr, 90% ee ^f	3j 81% Yield (1), 84% Yield (2)
1k	2k 86% Yield, 30:1 dr, 99% ee ^g	3k 86% Yield (1), 87% Yield (2)

^aYields are of material isolated by silica gel chromatography. Diastereo- and enantioselectivity were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

^b *n*BuLi was added at −78 °C.

^c MsCl (110 mol%), Et₃N (130 mol%) then NaH (400 mol%).

^dDiastereo- and enantioselectivity determined at the stage of the monotosylate.

^eNaH (200 mol%).

^fTHF (1.0 M).

^gDiastereo- and enantioselectivity determined for the corresponding monobenzoate.