Published in final edited form as:

Org Lett. 2009 July 16; 11(14): 3112–3115. doi:10.1021/ol901136w.

Elongation of 1,3-Polyols *via* Iterative Catalyst-Directed Carbonyl Allylation from the Alcohol Oxidation Level

Abbas Hassan, Yu Lu, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712

Abstract

Iterative enantioselective carbonyl allylation from the alcohol oxidation level under the conditions of iridium catalyzed transfer hydrogenation enables chain elongation of 1,3-polyols. High levels of catalyst-directed enantioselectivity and diastereoselectivity are observed.

In the course of exploring C-C bond forming hydrogenations beyond hydroformylation,¹ we recently found that iridium catalyzed transfer hydrogenation of allylic acetates or allenes in the presence of aldehydes results in highly enantioselective carbonyl allylation.^{2,3,4,5} Whereas reactions from the aldehyde oxidation level employ isopropanol as reductant, alcohols may serve dually as hydrogen donor and aldehyde precursor, enabling asymmetric carbonyl allylation,^{2a,b,e} crotylation^{2c} and reverse prenylation^{2d} directly from the alcohol oxidation level in the absence of any stoichiometric organometallic reagents.

In addition to the step economy associated with bypassing discrete alcohol oxidation and the pre-activation attending stoichiometric use of chiral allylmetal reagents, the ability to perform carbonyl allylation directly from the alcohol oxidation level enables allylations that are not easily achieved using aldehyde electrophiles. For example, whereas double asymmetric allylation of 1,3-diols delivers C₂-symmetric adducts with exceptional levels of optical enrichment,^{2e} corresponding allyl additions employing malondialdehydes are unknown. Based on this unique capability, an iterative two-directional elongation of 1,3-diols to furnish 1,3-

E-mail: mkrische@mail.utexas.edu.

Supporting Information Available. Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS). This material is available free of charge *via* the internet at <http://pubs.acs.org>.

polyols was achieved.^{6, 7} Here, we report related one-directional chain elongations employing mono-protected 1,3-diols as starting materials. In all cases, high levels of catalyst-directed enantioselectivity and diastereoselectivity are observed.⁸ This protocol, which involves iterative allylation from the alcohol oxidation level, avoids β -alkoxy aldehyde intermediates, which are often unstable with respect to elimination.

Our initial studies focused on the asymmetric allylation of *O*-benzyl 1,3-propylene glycol **1a**. Under previously reported conditions employing the cyclometallated catalyst generated *in situ* from [Ir(cod)Cl]₂, (*S*)-Cl₂MeO-BIPHEP and 3-nitrobenzoic acid,^{2b} the coupling of allyl acetate (1000 mol%) to **1a** at 120 °C delivers the homoallyl alcohol **2a** in 82% isolated yield and 94% enantiomeric excess (Table 1, entry 1). Lowering the reaction temperature to 100 °C slightly enhanced the degree of optical enrichment, but decreased the isolated yield of **2a** (Table 1, entry 2). At 120 °C, a decrease in the loading of allyl acetate from 10 to 5 equivalents diminished the isolated yield of **2a** by only 8% (Table 1, entries 1 and 3). However, upon a further decrease in the loading of allyl acetate from 5 to 2 equivalents, the isolated yield was unchanged (Table 1, entries 3 and 4). Finally, using the iridium *C,O*-benzoate generated *in situ* from [Ir(cod)Cl]₂, (*S*)-Cl₂MeO-BIPHEP and 4-chloro-3-nitrobenzoic acid, the homoallyl alcohol **2a** is obtained in 88% isolated yield and 95% enantiomeric excess (Table 1, entry 5). As decreased reaction temperature (100 °C) or extended reaction time (40 hours) did not improve this result (Table 1, entries 6 and 7), the latter conditions employing the catalyst modified by 4-chloro-3-nitrobenzoic acid at 120 °C were selected for iterative homologation of **2a** to form higher 1,3-polyols (Table 1, entry 5).

The iterative synthesis of higher 1,3-polyols requires exceptional levels of catalyst-directed diastereoselectivity. To explore this prospect, homoallyl alcohol **2a** was converted to the corresponding *tert*-butyldimethylsilyl ether **2b** and subjected to ozonolysis in methanol solvent employing a small quantity of Sudan III as indicator (3–5 drops of a 1.5 mM solution in methanol).⁹ Upon complete consumption of **2b**, as revealed through the change from a pink to a colorless solution, the reaction mixture was treated with sodium borohydride to deliver the alcohol **2c** in 92% isolated yield. Upon exposure of **2c** to the allylation conditions optimized for compound **1a** (Table 1) employing the catalyst modified by (*S*)-Cl₂MeO-BIPHEP at 120 °C, the product of carbonyl allylation (*R,S*)-**3a** was obtained in 55% isolated yield as 15:1 ratio of diastereomers. By lowering the reaction temperature to 100 °C and extending the reaction time to 40 hours under otherwise identical conditions, (*R,S*)-**3a** was obtained in 79% isolated yield as a 17:1 ratio of diastereomers. Under these same conditions, but using the catalyst modified by (*R*)-Cl₂MeO-BIPHEP, the diastereomeric adduct (*R,R*)-**3a** was obtained in 71% isolated yield as a 15:1 ratio of diastereomers. Upon use of the achiral iridium catalyst ligated BIPHEP, (*R,S*)-**3a** and (*R,R*)-**3a** are produced in an equimolar ratio (Scheme 1).

With compounds (*R,S*)-**3a** and (*R,R*)-**3a** in hand, the stereoselective synthesis of higher homologues was undertaken. Exposure of (*R,S*)-**3a** or (*R,R*)-**3a** to methanol in the presence of *p*-toluenesulfonic acid (10 mol%) with subsequent introduction of 2,2-dimethoxypropane delivers the diastereomeric acetonides (*R,S*)-**3b** and (*R,R*)-**3b**, respectively, which are isolated as single diastereomers. Ozonolysis of (*R,S*)-**3b** and (*R,R*)-**3b** followed by NaBH₄ reduction in accordance with the aforementioned procedure⁹ provides (*R,S*)-**3c** and (*R,R*)-**3c**. Transfer hydrogenative carbonyl allylation of (*R,S*)-**3c** or (*R,R*)-**3c** employing the catalyst modified by (*S*)-Cl₂MeO-BIPHEP at 100 °C delivers the products of carbonyl allylation (*R,S,S*)-**4a** and (*R,R,S*)-**4a**, respectively. Using the enantiomeric catalyst modified by (*R*)-Cl₂MeO-BIPHEP, (*R,S*)-**3c** or (*R,R*)-**3c** are transformed to homoallylic alcohols (*R,S,R*)-**4a** and (*R,R,R*)-**4a**, respectively. In each case, the minor diastereomer could not be detected by ¹H NMR analysis. Upon use of the achiral iridium catalyst ligated BIPHEP, (*R,S*)-**3c** and (*R,R*)-**3c** are converted to equimolar quantities of (*R,S,S*)-**4a**, (*R,S,R*)-**4a** and (*R,R,S*)-**4a**, (*R,R,R*)-**4a**, respectively (Scheme 1).

To illustrate the utility of this methodology in a related context, *O*-*p*-methoxybenzyl neopentyl glycol **5a** was subjected to transfer hydrogenative carbonyl allylation employing the catalyst modified by (*R*)-Cl,MeO-BIPHEP at 120 °C. The homoallylic alcohol **6a** was produced in 80% isolated yield and 95% enantiomeric excess. Conversion of **6a** to the *tert*-butyldimethylsilyl ether **6b**, followed by removal of the *p*-methoxybenzyl ether delivers the primary neopentyl alcohol **6c**. Transfer hydrogenative carbonyl allylation of **6c** employing the catalyst modified by (*R*)-Cl,MeO-BIPHEP at 120 °C provides the homoallyl alcohol (*R,R*)-**7a** in 78% isolated yield in a 12:1 diastereomeric ratio. Using the catalyst modified by (*S*)-Cl,MeO-BIPHEP at 120 °C, **6c** is converted to the homoallyl alcohol (*S,R*)-**7a** in 82% isolated yield in an 11:1 diastereomeric ratio. Using the achiral iridium catalyst modified by BIPHEP, (*R,R*)-**7a** and (*S,R*)-**7a** are formed in roughly equal proportion. Thus, catalyst-directed chain elongation may be conducted from either terminus of the 1,3-diol precursor with equal efficiency (Scheme 2).

In summary, under the conditions of transfer hydrogenative carbonyl allylation, the stereochemical bias of enantiomeric iridium catalysts modified by (*R*)-or (*S*)-Cl,MeO-BIPHEP is found to override the intrinsic diastereofacial bias of transient β -chiral aldehydes. Based on this finding, a concise enantio- and diastereoselective synthesis of 1,3-polyols was achieved via iterative chain elongation. The utility of this approach stems from the ability to circumvent use of chirally modified allylmethyl reagents, which require multi-step preparation, and the ability to perform chain elongation directly from the alcohol oxidation level, which avoids discrete generation of β -alkoxy aldehydes that are often unstable. Future studies will focus on the development of related C-C bond forming transfer hydrogenations, including imine additions from the amine oxidation level.¹⁰

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Acknowledgment is made to the Robert A. Welch Foundation, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable, and the NIH-NIGMS (RO1-GM069445) for partial support of this research. The Higher Education Commission, Pakistan is acknowledged for generous fellowship support (AH). Dr. Oliver Briel of Umicore is thanked for the generous donation of [Ir(cod)Cl]₂.

References

1. For selected reviews on C-C bond forming hydrogenation and transfer hydrogenation, see: (a)Ngai MY, Kong JR, Krische MJ. J Org Chem 2007;72:1063. [PubMed: 17288361](b)Skucas E, Ngai MY, Komanduri V, Krische MJ. Acc Chem Res 2007;40:1394. [PubMed: 17784728](c)Shibahara F, Krische MJ. Chem Lett 2008;37:1102.(d)Bower JF, Kim IS, Patman RL, Krische MJ. Angew Chem Int Ed 2009;48:34.
2. For enantioselective carbonyl allylation, crotylation and reverse prenylation via iridium catalyzed transfer hydrogenation, see: (a)Kim IS, Ngai MY, Krische MJ. J Am Chem Soc 2008;130:6340. [PubMed: 18444616](b)Kim IS, Ngai MY, Krische MJ. J Am Chem Soc 2008;130:14891. [PubMed: 18841896](c)Kim IS, Han SB, Krische MJ. J Am Chem Soc 2009;131:2514. [PubMed: 19191498](d) Han SB, Kim IS, Han H, Krische MJ. J Am Chem Soc 2009;131:6916. [PubMed: 19453190](e)Lu Y, Kim IS, Hassan A, Del Valle DJ, Krische MJ. Angew Chem Int Ed 2009;48 In Press.
3. For reviews on enantioselective carbonyl allylation, see: (a)Yamamoto Y, Asao N. Chem Rev 1993;93:2207.(b)Ramachandran PV. Aldrichim Acta 2002;35:23.(c)Kennedy JWJ, Hall DG. Angew Chem Int Ed 2003;42:4732.(d)Denmark SE, Fu J. Chem Rev 2003;103:2763. [PubMed: 12914480] (e)Yu CM, Youn J, Jung HK. Bull Korean Chem Soc 2006;27:463.(f)Marek I, Sklute G. Chem Commun 2007:1683.(g)Hall DG. Synlett 2007:1644.
4. For selected reviews of carbonyl allylation based on the reductive coupling of metallo- π -allyls derived from allylic alcohols, ethers or carboxylates, see: (a)Masuyama Y. Lanny S. Palladium-Catalyzed

Carbonyl Allylation via p-Allylpalladium Complexes. *Advances in Metal-Organic Chemistry*; Liebeskind JAI Press Greenwich 1994;3:255–303.303(b)Tamaru Y. Negishi, Eii; Meijere, Armin de Palladium-Catalyzed Reactions of Allyl and Related Derivatives with Organoelectrophiles. *Handbook of Organopalladium Chemistry for Organic Synthesis* Wiley New York 2002;2:1917–1943.1943(c)Tamaru Y. Tsuji J. Novel Catalytic Reactions involving p-Allylpalladium and -Nickel as the Key Intermediates: Umpolung and β -Decarbopalladation of p-Allylpalladium and Nickel-Catalyzed Homoallylation of Carbonyl Compounds with 1,3-Dienes. *Perspectives in Organopalladium Chemistry for the XXI Century* Elsevier Amsterdam 1999:215–231.231(d)Kondo T, Mitsudo T-a. *Curr Org Chem* 2002;6:1163.(e)Tamaru Y. *Eur J Org Chem* 2005;13:2647.(f)Zanoni G, Pontiroli A, Marchetti A, Vidari G. *Eur J Org Chem* 2007;22:3599.

5. For selected examples of carbonyl allylation via catalytic Nozaki-Hiyama-Kishi coupling of allylic halides, see: (a)Füerstner A, Shi N. *J Am Chem Soc* 1996;118:2533.(b)Bandini M, Cozzi PG, Umani-Ronchi A. *Polyhedron* 2000;19:537.(c)McManus HA, Cozzi PG, Guiry PJ. *Adv Synth Catal* 2006;348:551.(d)Hargaden GC, Müller-Bunz H, Guiry PJ. *Eur J Org Chem* 2007:4235.(e)Hargaden GC, O'Sullivan TP, Guiry PJ. *Org Biomol Chem* 2008;6:562. [PubMed: 18219428]
6. For a review on two-directional chain elongation in target-oriented synthesis, see: Poss CS, Schreiber SL. *Acc Chem Res* 1994;27:9.
7. For selected reviews of the synthesis of 1,3-diol substructures, see: (a)Masamune S, Choy W. *Aldrichim Acta* 1982;15:47.(b)Oishi T, Nakata T. *Synthesis* 1990:635.(c)Schneider C. *Angew Chem Int Ed* 1998;37:1375.(d)Bode SE, Wohlberg M, Müller M. *Synthesis* 2006:557.
8. For selected examples of catalyst directed diastereoselectivity, see: (a)Minami N, Ko SS, Kishi Y. *J Am Chem Soc* 1982;104:1109.(b)Ko SY, Lee AWM, Masamune S, Reed LA III, Sharpless KB, Walker FJ. *Science* 1983:949. [PubMed: 17816019](c)Kobayashi S, Ohtsubo A, Mukaiyama T. *Chem Lett* 1991:831.(d)Hammadi A, Nuzillard JM, Poulin JC, Kagan HB. *Tetrahedron: Asymmetry* 1992;3:1247.(e)Doyle MP, Kalinin AV, Ene DG. *J Am Chem Soc* 1996;118:8837.(f)Trost BM, Calkins TL, Oertelt C, Zambrano J. *Tetrahedron Lett* 1998;39:1713.(g)Balskus EP, Jacobsen EN. *Science* 2007;317:1736. [PubMed: 17885133](h)Han SB, Kong JR, Krische MJ. *Org Lett* 2008;10:4133. [PubMed: 18729371]
9. Veysoglu T, Mitscher LA, Swayze JK. *Synthesis* 1980:807.
10. The collective alcohol-unsaturate C-C coupling we describe (ref. 1c,d) may be viewed as “hydrohydroxyalkylations.” For related amine-unsaturate C-C coupling, or “hydroaminoalkylation,” see: (a)Maspero F, Clerici MG. *Synthesis* 1980:305.(b)Nugent WA, Ovenall DW, Homes SJ. *Organometallics* 1983;2:161.(c)Herzon SB, Hartwig JF. *J Am Chem Soc* 2007;129:6690. [PubMed: 17474747](d)Herzon SB, Hartwig JF. *J Am Chem Soc* 2008;130:14940. [PubMed: 18937477](e)Kubiak R, Prochnow I, Doye S. *Angew Chem Int Ed* 2009;48:1153.(f)Bexrud JA, Eisenberger P, Leitch DC, Payne PR, Schafer LL. *J Am Chem Soc* 2009;131:2116. [PubMed: 19173650]

Scheme 1.

Catalyst-directed diastereoselectivity in the transfer hydrogenative carbonyl allylation of **2c** and synthesis of higher homologues **4a**.^a

^aSee Supporting Information for experimental details.

Scheme 2. Transfer hydrogenative chain elongation from both termini of neopentyl glycol **5a**.^aSee supporting information for experimental details.

Table 1
Asymmetric transfer hydrogenative carbonyl allylation of *O*-benzyl 1,3-propylene glycol **1a**.

entry	acid additive	allyl acetate	temp °C	yield (%)	ee (%)	
1	3-N ₂ -BzOH	1000 (mol %)	120	82	94 (S)	
2	3-NO ₂ -BzOH	1000 (mol %)	100	76	96 (S)	
3	3-NO ₂ -BzOH	500 (mol %)	120	74	94 (S)	
4	3-NO ₂ -BzOH	200 (mol %)	120	74	95 (S)	
⇒5	4-Cl-3-NO₂-BzOH	200 (mol %)	120	88	95 (S)	
6	4-Cl-3-NO ₂ -BzOH	200 (mol %)	100	45	95 (S)	
7^b	4-Cl-3-NO ₂ -BzOH	200 (mol %)	100	79	95 (S)	

^a All reactions were performed in 13 × 100 mm pressure tubes. The cited yields are of material isolated by silica gel chromatography and represent the average of two runs. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for experimental details.

^b The reaction was allowed to proceed for 40 hours.