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Asymmetric Allylation of Glycidols Mediated by Allyl Acetate via Iridium-Catalyzed Hydrogen Transfer

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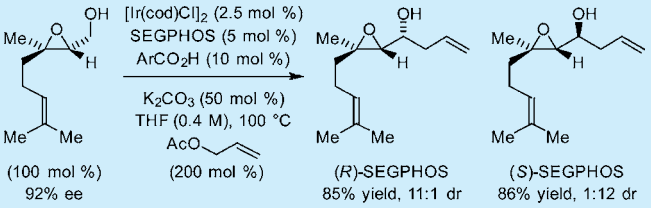
Supporting Information

ABSTRACT: Glycidols prepared via Sharpless asymmetric epoxidation participate in asymmetric redox-neutral carbonyl allylation with good levels of catalyst-directed diastereoselectivity. Equally stereoselective allylations may be performed from the aldehyde oxidation level using 2-propanol as the terminal reductant. An epoxide ring-opening reaction using $AlMe_3$-*n*-BuLi is used to prepare the propionate-based stereotetrad spanning C17−C23 of dictyostatin, illustrating how this method may be applied to polyketide construction.



Epoxides are important building blocks in chemical synthesis, including the construction of polyketide natural products where they also appear as native structural motifs.[1] Accordingly, several methods have been reported for the asymmetric allylation[2] of glycidic aldehydes using reagents based on boron,[3,4] tin,[5,6] silicon,[7,8] indium,[9] and magnesium.[10] These methods have proven effective in certain contexts;[3−10] however, due to pronounced match−mismatch effects, only one diastereomer of the secondary homoallylic glycidol is generally accessible in highly diastereomerically enriched form.[11] Additionally, indirect formation of secondary homoallylic glycidols via enantioselective allylation of α,β-unsaturated aldehydes followed by Sharpless asymmetric epoxidation is problematic, as modest diastereoselectivities are evident in reactions of secondary (*Z*)-allylic alcohols.[12]

By harnessing the native reducing ability of alcohols, we have discovered a new, redox-economic class of C−C bond formations that merge the characteristics of carbonyl addition and transfer hydrogenation.[13] These hydrogen autotransfer processes utilize alcohol oxidation to drive reductive generation of transient organometallic nucleophiles. The resulting carbonyl−organometal pair combines to furnish products of addition, directly converting lower alcohols to higher alcohols. Based on this pattern of reactivity, diverse enantioselective alcohol C−H functionalizations have been developed including the C−H allylation[14] and crotylation[15,16] of primary alcohols to form secondary homoallylic alcohols. In the present account, this allylation method is applied to the conversion of primary glycidols to secondary homoallylic glycidols.

Initial studies were focused on the allylation of glycidol **1a**, which is prepared through Sharpless asymmetric epoxidation of geraniol.[17] For the sake of convenience, the cyclometalated π-allyliridium *C*,*O*-benzoate catalysts were generated *in situ* from commercial components. Thus, glycidol **1a** was exposed to allyl acetate in the presence of $[Ir(cod)Cl]_2$, a series of 4-substituted 3-nitro-benzoic acids, assorted axially chiral chelating phosphine ligands, and various inorganic bases. A small set of optimization experiments quickly led to the identification of effective conditions. Thus, using the iridium catalysts (*R*)- or (*S*)-Ir-**I** modified by SEGPHOS, the diastereomeric secondary homoallylic glycidols **2a** and *epi*-**2a** were obtained in excellent yields and diastereoselectivities, respectively (Table 1). Notably, unlike the corresponding allylborations,[11] the enantiomeric catalysts delivered **2a** and *epi*-**2a** with roughly equivalent levels of catalyst-directed diastereoselectivity (**2a**/*epi*-**2a** = 11:1 vs 1:12), suggesting the present iridium catalysts are insensitive to match−mismatch effects. Indeed, using an achiral iridium catalyst modified by dppf, a 1:1 mixture of diastereomeric secondary homoallylic glycidols **2b** and *epi*-**2b** was obtained.

The identification of favorable conditions for the asymmetric C−H allylation of glycidol **1a** prompted a more detailed investigation into the scope of this process (Table 1). *cis*-Glycidols **1b−e** were specifically selected for study as the corresponding secondary homoallylic glycidols **2b−e** and *epi*-**2b**−*epi*-**2e** are inaccessible using conventional allylation methods[2−10] due to the modest diastereoselectivities reported in Sharpless asymmetric epoxidations of secondary (*Z*)-allylic alcohols[12] along with the stereochemically labile nature of (*Z*)-α,β-unsaturated aldehydes. In the event, *cis*-glycidols **1b−e** were converted to the secondary homoallylic glycidols **2b−e** and *epi*-**2b**−*epi*-**2e**, respectively, in good yields and good levels of catalyst-directed diastereoselectivity. In certain cases, the iridium catalysts (*R*)- or (*S*)-Ir-**II** modified by Cl,MeO-BIPHEP were found to enforce higher yields and diastereoselectivities than the iridium catalysts (*R*)- or (*S*)-Ir-**I** modified by SEGPHOS. To complete this study, the allylation of *trans*-glycidol **1f** was explored. Whereas secondary homoallylic glycidol **2f** was formed with excellent levels of catalyst-directed diastereoselectivity, the isomeric glycidol *epi*-**2f** was formed in low yield with less pronounced levels of stereocontrol.

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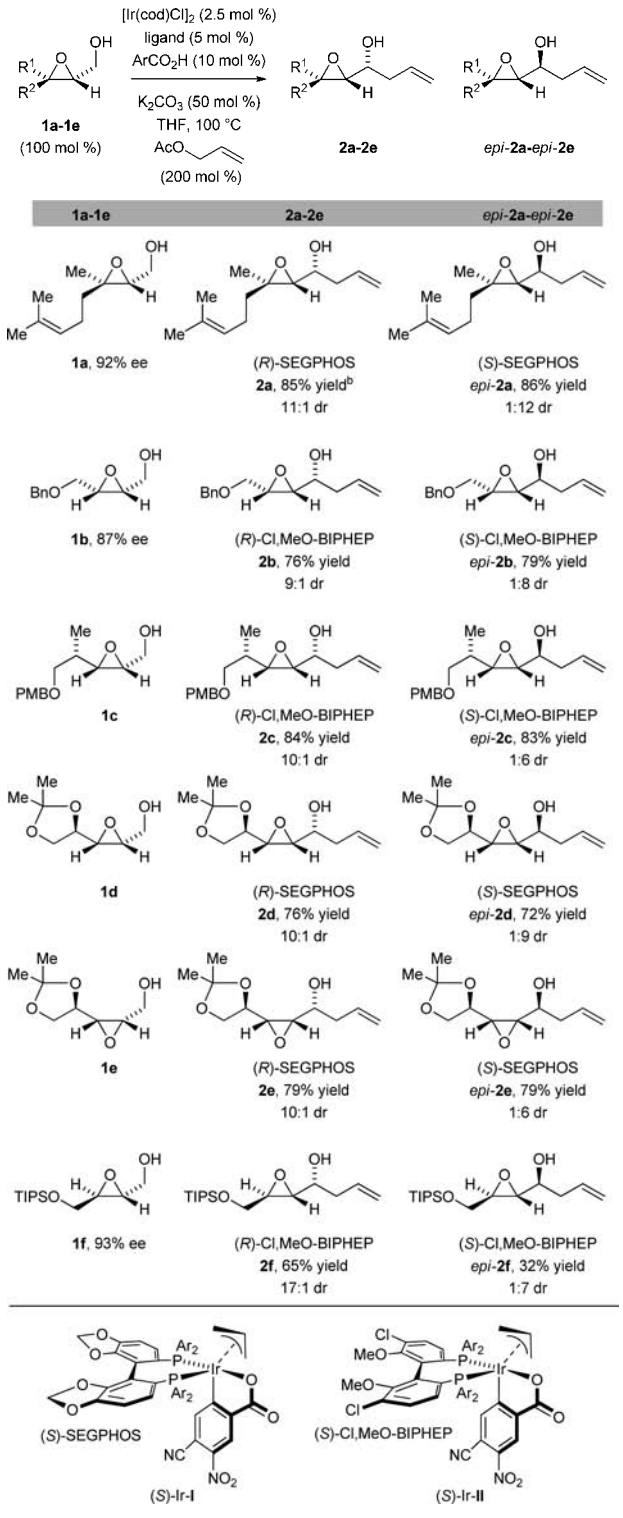
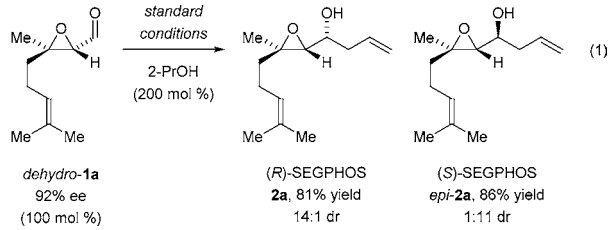
Table 1. Iridium-Catalyzed C−H Allylation of Glycidols 1a−f To Form Adducts 2a−f and *epi*-2a−f[a]



[a]Cited yields are of material isolated by silica gel chromatography. $ArCO_2H$ refers to 4-cyano-3-nitrobenzoic acid. Diastereomeric ratios were determined by ^1H NMR of crude reaction mixtures. See the Supporting Information for further experimental details. [b]On a 1 mmol scale, **2a** is formed in 81% yield and 10:1 dr.

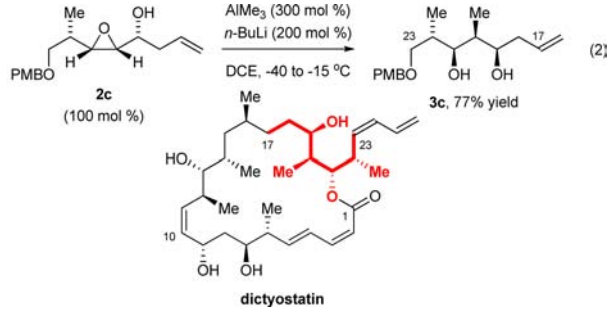
These data suggest match−mismatch effects may be more important in reactions of *trans*-glycidols. Finally, it is worth noting that due to the Horeau principle, all major reaction products derived from **1a**, **1b**, and **1f**, are obtained in >99% enantiomeric excess.[18]

The direct C−H allylation of primary glycidols **1a−e** is both step-economic and redox-economic as it avoids discrete formation and isolation of less tractable glycidic aldehydes. Nevertheless, under certain circumstances it may be desirable to conduct the allylation from the aldehyde oxidation level. To assess the feasibility of utilizing glycidic aldehydes as reactants, the reductive coupling of allyl acetate with *dehydro*-**1a** was performed using 2-propanol as the terminal reductant under otherwise standard conditions (eq 1). The respective secondary



homoallylic glycidols **2a** and *epi*-**2a** were formed in good yields with excellent levels of catalyst-directed diastereoselectivity. The efficiencies observed in the reactions of glycidic aldehyde *dehydro*-**1a** were roughly equivalent to those observed using the corresponding glycidol **1a** (Table 1).

To illustrate how the present method may be applied to polyketide construction, secondary homoallylic glycidol **2c** was subjected to conditions for regioselective epoxide ring opening using $AlMe_3$−*n*-BuLi (eq 2).[19] The desired adduct **3c**, which



was obtained in 77% yield, embodies a propionate-based stereotetrad spanning C17−C23 of dictyostatin, a marine macrolide that displays antimitotic activity against multidrug-resistant cancer cell lines at nanomolar levels.[20,21]

In summary, we report that glycidols prepared through Sharpless asymmetric epoxidation participate in direct carbinol C−H allylation with excellent levels of catalyst-directed diastereoselectivity. This method is redox- and step-economic, as it avoids discrete formation of less tractable glycidic aldehydes. Further, this method overcomes limitations evident in corresponding allylations of glycidic aldehydes using allylboron reagents.[3a,b,11] Finally, as Sharpless asymmetric epoxidations of secondary (*Z*)-allylic alcohols display low levels of diastereoselectivity,[12] indirect formation of the present secondary homoallylic glycidols through an asymmetric enal allylation−epoxidation sequence is not feasible. Future studies will focus on the use of α-olefins[22] as pronucleophiles in alcohol-mediated carbonyl addition.

■ ASSOCIATED CONTENT

Supporting Information

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Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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DEDICATION

This work is dedicated to Professor Teruaki Mukaiyama in celebration of his 90th birthday (Sotsuju).

REFERENCES

(1) For selected reviews on the use of glycidic alcohols and aldehydes in chemical synthesis, see: (a) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (b) Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359. (c) Riera, A.; Moreno, M. *Molecules* **2010**, *15*, 1041.

(2) For selected reviews on enantioselective carbonyl allylation, crotylation, and related processes, see: (a) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (d) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (e) Hall, D. G. *Synlett* **2007**, *2007*, 1644. (f) Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407. (g) Lachance, H.; Hall, D. G. *Org. React.* **2009**, *73*, 1. (h) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Commun.* **2009**, 7278. (i) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (j) Moran, J.; Krische, M. J. In *Asymmetric Synthesis − The Essentials II*; Christmann, M., Bräse, S., Eds.; Wiley-VCH: Weinheim, 2012; p 187. (k) Shin, I.; Krische, M. J. *Top. Curr. Chem.* **2015**, *372*, 85. (l) Feng, J.; Kasun, Z. A.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 5467.

(3) For methodological studies of the allylboron of glycidic aldehydes, see: (a) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (b) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636. (c) Nowrouzi, F.; Janetzko, J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 5490.

(4) For applications of glycidic aldehyde allylboration in natural product synthesis, see: (a) Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Synlett* **2004**, *15*, 2830. (b) García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A.; Matesanz, R.; Díaz, J. F.; Barasoain, I. *Chem. - Eur. J.* **2007**, *13*, 5060. (c) Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Org. Chem.* **2009**, *74*, 230. (d) Murata, T.; Sano, M.; Takamura, H.; Kadota, I.; Uemura, D. *J. Org. Chem.* **2009**, *74*, 4797. (e) Yadav, J. S.; Das, S. K.; Sabitha, G. *J. Org. Chem.* **2012**, *77*, 11109.

(5) For methodological studies of the allylstannylation of glycidic aldehydes, see: (a) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629. (b) Fernández de la Pradilla, R. F.; Castellanos, A.; Fernández, J.; Lorenzo, M.; Manzano, P.; Méndez, P.; Priego, J.; Viso, A. *J. Org. Chem.* **2006**, *71*, 1569.

(6) For applications of glycidic aldehyde allylstannylation in natural product synthesis, see: (a) Jørgensen, K. B.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8855. (b) Bartlett, L.; Gross, L.; Péron, F.; Asby, D. J.; Selby, M. D.; Tavassoli, A.; Linclau, B. *Chem. - Eur. J.* **2014**, *20*, 3306.

(7) For methodological studies of the allylsilylation of glycidic aldehydes, see: Wang, S.; Howe, G. P.; Mahal, R. S.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3351.

(8) For applications of glycidic aldehyde allylsilylation in natural product synthesis, see: Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128.

(9) For methodological studies of the allylindiation of glycidic aldehydes, see: (a) Paquette, L. A.; Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863. (b) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

(10) For methodological studies of the allylmagnesiation of glycidic aldehydes, see: (a) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728. (b) Urabe, H.; Matsuka, T.; Sato, F. *Tetrahedron Lett.* **1992**, *33*, 4179.

(11) A systematic investigation of match−mismatch effects may be found in ref 3a,b.

(12) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(13) For selected reviews on catalytic carbonyl addition via alcohol-mediated hydrogen autotransfer, see: (a) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (b) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504. (c) Perez, F.; Oda, S.; Geary, L. M.; Krische, M. J. *Top. Curr. Chem.* **2016**, *374*, 365.

(14) For iridium catalyzed enantioselective C−H allylation of primary alcohols, see: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (d) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. (e) Schmitt, D. C.; Dechert-Schmitt, A.-M. R.; Krische, M. J. *Org. Lett.* **2012**, *14*, 6302. (f) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3195. (g) Shin, I.; Wang, G.; Krische, M. J. *Chem. - Eur. J.* **2014**, *20*, 13382. (h) Liang, T.; Zhang, W.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 16024.

(15) For iridium catalyzed enantioselective C−H crotylation of primary alcohols, see: (a) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (b) Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350. (c) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795.

(16) For ruthenium-catalyzed enantioselective C−H crotylation of primary alcohols, see: (a) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582. (b) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324. (c) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 20628. (d) Liang, T.; Zhang, W.; Chen, T.-Y.; Nguyen, K. D.; Krische, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 13066.

(17) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(18) (a) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055. (b) For a historical review, see: Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 495. A 99.5% enantiomeric excess was established for glycidols **2b** through chiral stationary-phase HPLC analysis. See the Supporting Information for further experimental details..

(19) (a) Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* **2001**, *3*, 1765. (b) Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. *Org. Lett.* **2007**, *9*, 1895.

(20) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1111. (b) Pettit, G. R.; Cichacz, Z. A. WO 5430053, 1995; *Chem. Abstr.* **1995**, 733500. (c) Isbrucker, R. A.; Cummins, J.; Pomponi, S. A.; Longley, R. E.; Wright, A. E. *Biochem. Pharmacol.* **2003**, *66*, 75.

(21) (a) Pfeiffer, B.; Kuzniewski, C. N.; Wullschleger, C.; Altmann, K.-H. *Top. Curr. Chem.* **2009**, *286*, 1. (b) Dalby, S. M.; Paterson, I. *Curr. Opin. Drug Disc. Devel.* **2010**, *13*, 777.

(22) For a review on the metal-catalyzed reductive coupling of olefin-derived nucleophiles, see: Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. *Science* **2016**, *354*, 300.

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