JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Iridium-Catalyzed Enantioselective Polyene Cyclization

Michael A. Schafroth,[†] David Sarlah,[†] Simon Krautwald, and Erick M. Carreira*

Eidgenössische Technische Hochschule Zürich, HCI H335, 8093 Zürich, Switzerland

Supporting Information

ABSTRACT: A highly enantioselective polycyclization method has been developed using the combination of Lewis acid activation with iridium-catalyzed allylic substitution. This strategy relies on direct use of branched, racemic allylic alcohols and furnishes a diverse and unique set of carbo- and heteropolycyclic ring systems in good yields and ≥99% ee.

Almost six decades ago, Eschenmoser and Stork pointed out that the stereochemical course of the biogenetic cyclizations of polyenes could be rationalized on the basis of stereoelectronic considerations.[1] The hypothesis known as the biogenic isoprene rule stimulated extensive nonenzymatic, biomimetic studies and created one of the most powerful methods for the rapid construction of polycyclic frameworks.[2] Despite substantial efforts in this field, only a limited number of catalytic enantioselective cyclizations have been developed to date. These include the use of Brønsted/Lewis acid catalysis by Yamamoto, Loh, and Corey[3] as well as organocatalysis by Ishihara, MacMillan, and Jacobsen.[4] In contrast, transition-metal-catalyzed enantioselective polycyclizations have received significantly less attention. Gagné has reported a platinum-catalyzed cyclization of alkenes,[5] and Toste has developed a gold-catalyzed cyclization of alkynes.[6] Following the seminal achievements of Takeuchi, Helmchen, and Hartwig,[7] iridium is now employed with a wide range of nucleophiles in the allylic substitution reaction.[8] We have reported a number of substitution reactions[9] characterized by atom economy.[10] Herein, we describe a new enantioselective polyene cyclization cascade from unactivated, branched racemic allylic alcohols enabled by an Ir(P,olefin) complex (Scheme 1).[11] As the first report of the use of allyl alcohols as initiators in enantioselective polycyclizations,[12] these results serve as proof-of-principle for the use of allyl-metal species in polyene cyclizations.

Our study of the Ir-catalyzed polycyclization began by evaluating the reaction of **1a** as a test substrate under conditions

Scheme 1. Ir-Catalyzed Enantioselective Cyclization

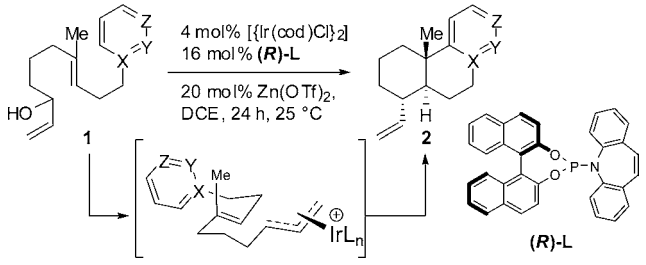
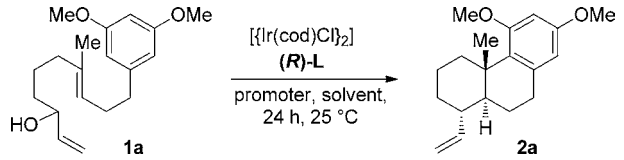


Table 1. Optimization of the Ir-Catalyzed Cyclization Reaction[a]



entry	promoter (mol%)	solvent	yield[b]	ee (%)[c]
1	$P(O)(OBu)_2OH$ (50)	$(CH_2Cl)_2$	42	89
2	$Bi(OTf)_3$ (10)	$(CH_2Cl)_2$	71	96
3	$Sc(OTf)_3$ (10)	$(CH_2Cl)_2$	91	80
4	$In(OTf)_3$ (10)	$(CH_2Cl)_2$	84	88
5	$Yb(OTf)_3$ (10)	$(CH_2Cl)_2$	79	94
6	$Zn(OTf)_2$ (10)	$(CH_2Cl)_2$	72	>99.5
7	$Zn(OTf)_2$ (10)	dioxane	8	>99.5
8	$Zn(OTf)_2$ (10)	DMF	n.r.	–
9	$Zn(OTf)_2$ (20)	$(CH_2Cl)_2$	90	>99.5
10	$Zn(OTf)_2$ (50)	$(CH_2Cl)_2$	83	99
11	TfOH (20)	$(CH_2Cl)_2$	12	81

[a]Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), [{Ir(cod)Cl}$_2$] (4 mol%), (*R*)-**L** (16 mol%), promoter, solvent (1.5 mL), 25 °C, 24 h. [b]Yield of **2a** after purification by chromatography. [c]Determined by SFC on a chiral stationary phase.

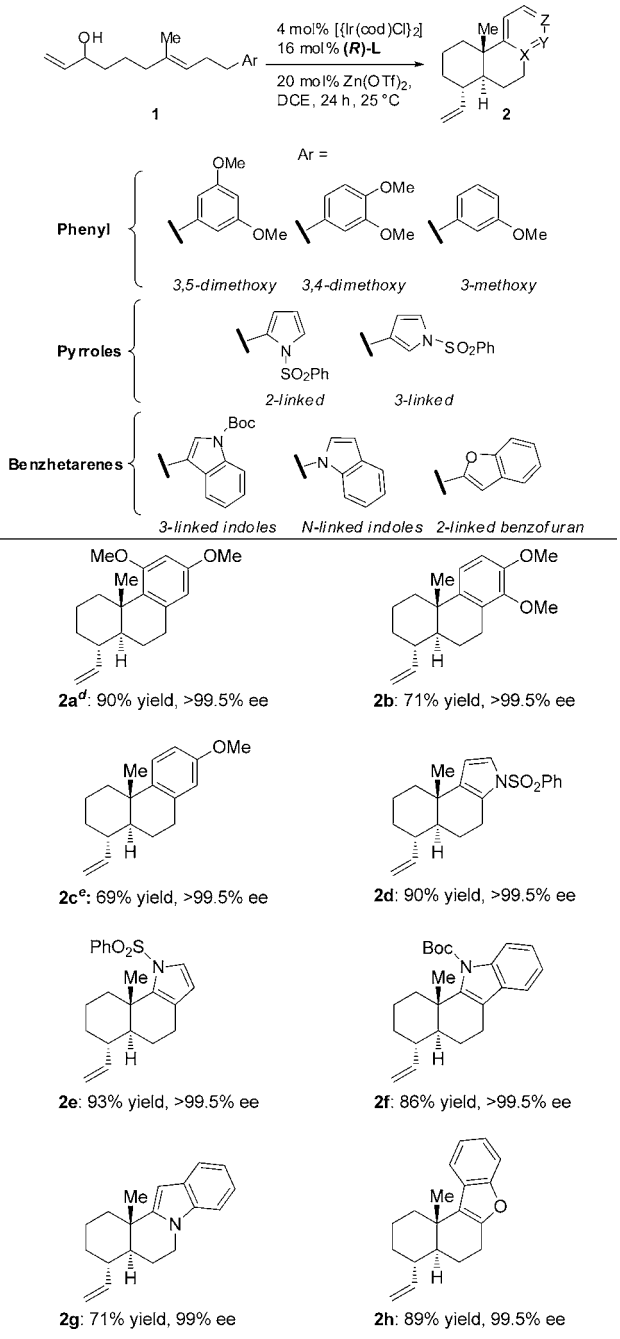
we have employed for allylic substitution with heteronucleophiles, such as amines, alcohols, and thiols, with added Brønsted acid activators (Table 1, entry 1). Exposure of **1a** to [{Ir(cod)Cl}$_2$] and (*R*)-**L** in the presence of di-*n*-butylphosphoric acid as a promoter in dichloroethane afforded tricyclic product **2a** in 42% yield and 89% ee. Further screening of various conditions using a variety of Brønsted acids did not significantly improve the reaction outcome (see Supporting Information, Table S2). Inspired by Shibasaki's insightful report that bismuth salts can efficiently catalyze allylic substitution of alcohols,[13] we turned our attention toward Lewis acids as potential promoters.[14] We observed that the use of 10 mol% $Bi(OTf)_3$ drastically improved conversion, leading to isolation of **2a** in 71% yield and 96% ee after 24 h at ambient temperature (Table 1, entry 2). Further screening of the reaction parameters, including metal triflates (Table 1, entries 3–6) and solvents (Table 1, entries 7 and 8, see Supporting Information Table S4), revealed that $Zn(OTf)_2$ in dichloroethane routinely afforded superb enantioselectivity, **2a** >99.5% ee (Table 1, entry 6).

The amount of $Zn(OTf)_2$ influenced the reaction outcome (Table 1, entries 6, 9, and 10): 20 mol% was found to be optimal,

Received: October 21, 2012
Published: November 29, 2012

   dx.doi.org/10.1021/ja310386m | *J. Am. Chem. Soc.* 2012, 134, 20276–20278

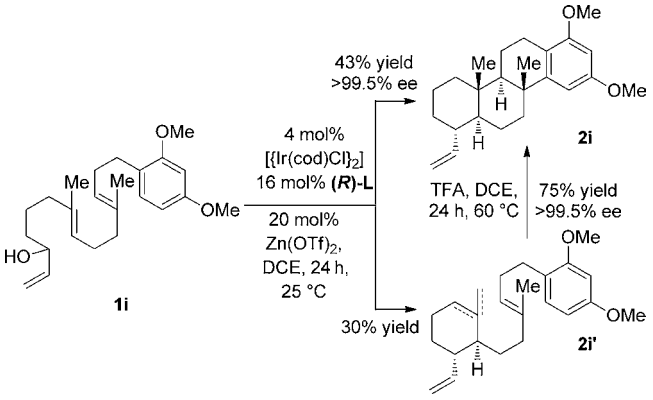
Table 2. Scope of the Ir-Catalyzed Polyene Cyclization[a,b,c]



[a]Standard procedure: Substrate **1** (0.5 mmol, 1.0 equiv), [{Ir(cod)-Cl}$_2$] (4 mol%), (***R***)-**L** (16 mol%), Zn(OTf)$_2$ (20 mol%), DCE (3.0 mL), 25 °C, 24 h. [b]Isolated yields after purification by flash chromatography. [c]Enantiomeric excess determined by SFC analysis on a chiral stationary phase; absolute configuration determined by correlation. [d]Run on 1.0 mmol scale. [e]Ortho/para mixture (1:2); 99% ee for the ortho regioisomer (not shown).

in terms of both yield and reaction time. Thus, under optimal conditions, tricyclic product **2a** could be isolated in 90% yield and >99.5% ee (Table 1, entry 9). It is important to note that the potential role of TfOH as the promoter, which could be generated from a triflate and adventitious H_2O, was excluded, because a low yield of product **2a** was observed when using TfOH as an additive (Table 1, entry 11). Additionally, reactions

Scheme 2. Ir-Catalyzed Tricyclization



performed with Zn(OTf)$_2$ and in the absence of Ir/(***R***)-**L** provided none of the desired cyclized product.

With optimized conditions in hand, we evaluated the scope of the cyclization. As shown in Table 2, the reaction proceeded well with a range of substrates, encompassing arenes as terminating nucleophiles and delivering a range of carbo- and heterocyclic ring systems. Thus, a number of alkoxy-substituted aromatics (**2a**−**2c**), pyrroles (**2d**, **2e**), indoles (**2f**, **2g**), and furan (**2h**) heterocycles all underwent cyclization in high yield and excellent enantioselectivity (ee's ≥ 99%). When the meta-methoxy substituted arene was used, cyclization at the para-position (**2c**, relative to methoxy group) was predominant, giving 1:2 ortho/para selectivity. This result is consistent with the literature precedent for cation-initiated cyclizations.[15] In each case the cyclization products were formed as single diastereoisomers, and no side products resulting from potentially competitive intermolecular processes were observed.[16] It is important to note that all the reactions are conducted at ambient temperature with commercial grade solvents and reagents, making this cyclization protocol convenient to perform. Lastly, this process can be scaled up without any erosion in yield and selectivity, as demonstrated in one example (1 mmol scale, **1a**→**2a**, Table 2).

To further test the potential of this Ir-catalyzed cyclization reaction, we turned our attention toward expanding beyond the bicyclization reactions discussed above and examining the corresponding tricyclization process. To this end, Ir-catalyzed cyclization of **1i** afforded tetracyclic product **2i** in 43% isolated yield and >99.5% ee as a single diastereomer (Scheme 2).[17] Careful separation of the reaction mixture revealed additional byproducts of similar polarity, which were identified as a mixture of isomeric **2i**′.[18] Although **2i**′ could not be induced to undergo cyclization to **2i** under the reaction conditions,[19] subsequent exposure of the latter to trifluoroacetic acid gave fully cyclized tetracycle **2i** in 75% yield (combined yield of 65%) and with identical enantioselectivity.[20] The observations summarized in Scheme 2 provide insight concerning the stereochemical course of the polycylization reaction **1i**→**2i**. The facts that the formation of **2i**′ from **1i** proceeds with high stereoselectivity and that in turn its cyclization under acidic conditions furnishes **2i** with complete stereoselectivity imply that the catalyst effects direct stereocontrol merely over the first cyclization event.[21] The stereoselectivity of the subsequent ring closure is then effectively encoded in the first ring, which proceeds selectively in accordance with the Stork−Eschenmoser paradigm.

In conclusion, we have disclosed the first example of a polyene cyclization reaction initiated by an Ir(P,olefin) catalyst through the formation of an allyl-metal intermediate to furnish

dx.doi.org/10.1021/ja310386m | J. Am. Chem. Soc. 2012, 134, 20276−20278

polycyclization products in >99% ee. This Ir-catalyzed, $Zn(OTf)_2$-promoted direct activation of allylic alcohols serves as an efficient, user-friendly, and scalable method for rapid and stereoselective construction of products, which are useful building blocks for terpenoids and pharmaceuticals. Further applications of the $[Ir]/Zn(OTf)_2$ system as well as mechanistic studies of the reaction are under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^1H and ^{13}C NMR spectra and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

carreira@org.chem.ethz.ch

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.K. thanks the Fonds der Chemischen Industrie for support (Chemiefonds-Stipendium).

■ REFERENCES

(1) (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (c) Stadler, P. A.; Eschenmoser, A.; Schinz, J. H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191. (d) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011.

(2) For a recent review, see: (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. For early contributions, see: (b) Johnson, W. S.; Kinnel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861. (c) van Tamelen, E. E.; McCormick, J. P. *J. Am. Chem. Soc.* **1969**, *91*, 1847. (d) Goldsmith, D. J.; Phillips, C. F. *J. Am. Chem. Soc.* **1969**, *91*, 5862.

(3) (a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (c) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (d) Zhao, Y.-J.; Li, B.; Tan, L.-J. S.; Shen, Z.-L.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 10242. (e) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992.

(4) (a) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (b) Rendeler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (c) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

(5) Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6011.

(6) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.

(7) (a) Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 263. (b) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025. (c) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.

(8) For recent reviews on this topic, see: (a) Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169. (b) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2012**, *38*, 155. (c) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147.

(9) (a) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (b) Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3470. (c) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5568. (d) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8652.

(10) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(11) For recent enantioselective Ir-catalyzed intramolecular C−C bond forming reactions, see: (a) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418. (b) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455. (c) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci.* **2012**, *3*, 205. (d) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 2579.

(12) For early reports on the use of allylic alcohols as initiating groups, see: (a) Johnson, W. S.; Semmelhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994. (b) Carney, R. L; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 2549.

(13) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

(14) For use of Lewis acids as activators of allylic alcohols in Ir-catalyzed allylic substitution, see: Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508.

(15) (a) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (b) See also Reference 2c.

(16) In all cases, the only detectable byproduct is a linear ethyl ketone, resulting from isomerization of the corresponding allylic alcohol.

(17) The relative stereochemistry of **2i** was secured by X-ray crystallography (see Supporting Information).

(18) In addition to monocyclized isomers, the mixture contained also some bicyclized products, as determined by ^1H NMR.

(19) Heating the reaction (**1i**→**2i**) or exposing **2i′** to $Zn(OTf)_2$ at elevated temperatures (**2i′**→**2i**) did not induce any further cyclization.

(20) For selected examples on TFA-mediated polyene cyclizations, see: (a) Schmid, R.; Huesmann, P. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1980**, *102*, 5122. (b) Johnson, W. S.; Lindell, S. D.; Steele, J. *J. Am. Chem. Soc.* **1987**, *109*, 5852.

(21) Ir-complexes are known to catalyze intramolecular ene-type reactions; however, to the best of our knowledge this is the first known example where a π-allyl-Ir species initiates this process with an isolated double bond.