Communication

An Ir/Zn Dual Catalysis for Enantio- and Diastereodivergent #-Allylation of #-Hydroxyketones

Xiaohong Huo, Rui He, Xiao Zhang, and Wanbin Zhang

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.6b06156 • Publication Date (Web): 22 Aug 2016

An Ir/Zn Dual Catalysis for Enantio- and Diastereodivergent α-Allylation of α-Hydroxyketones

Xiaohong Huo,[†,§] Rui He,[‡,§] Xiao Zhang,[‡] and Wanbin Zhang*[,†,‡]

[†]School of Pharmacy and [‡]School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China

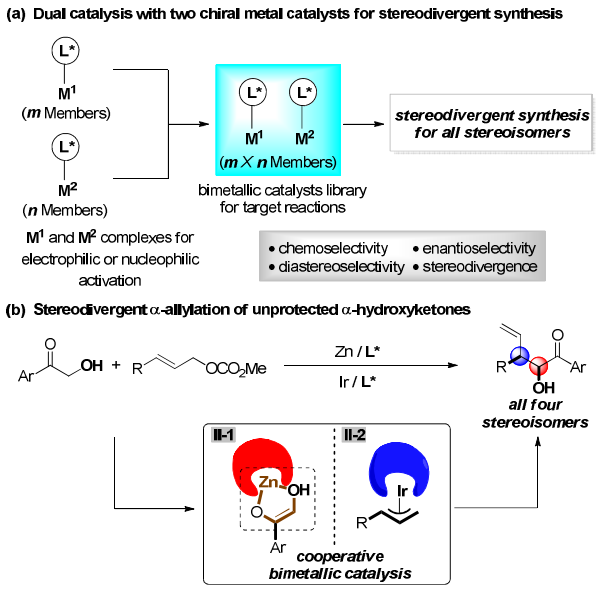
Supporting Information Placeholder

ABSTRACT: An Ir/Zn dual catalysis has been developed for the enantio- and diastereodivergent α-allylation of unprotected α-hydroxyketones under mild conditions, in the absence of any additional base. The cooperative action of a chiral iridium complex derived from phosphoramidites and a chiral Zn-ProPhenol complex is most likely responsible for its high reactivity, excellent enantioselectivity (up to >99% ee), and good diastereoselectivity (up to >20:1 dr). All four product stereoisomers could be prepared from the same set of starting materials and under identical conditions by simple selection of appropriate catalyst combinations.

Structural motifs containing contiguous stereogenic centers are found in numerous natural products and important bioactive compounds, and their absolute and relative configurations are often crucial for the expression of their biological activities.[1] The development of reliable methodologies that lead to all possible stereoisomers of products is a prominent research objective, as well as a significant challenge in asymmetric synthesis.[2] Many classical strategies have attempted to address this challenge via the use of additives,[3] the selection of distinct catalysts,[4] and the use of two-step sequential reactions with one or two chiral catalysts.[5] However, few methodologies are able to provide a unified and predictable route that exerts full control of the absolute and relative stereochemical configuration of products containing multiple contiguous stereocenters. Recently, Carreira and colleagues developed an elegant dual catalyst system for the independent control of two stereocenters in the α-allylation of aldehydes by combining iridium and organic catalysis.[6-7] However, the development of a cooperative bimetallic catalyst system that utilizes two distinct chiral metal catalysts for the complete stereoisomeric control of products bearing multiple stereocenters remains underdeveloped but is highly desired.[8] This desirability resides in: (a) the abundance of ready-made or commercially available chiral ligands and metal catalysts;[9] (b) diverse asymmetric reactions involving metal catalysis;[10] and (c) a large bimetallic catalyst library created via random combination of two different chiral metal catalysts for targeted asymmetric metal catalysis (Scheme 1a).

Ir-catalyzed allylic substitution has become one of the most powerful methods to construct carbon-carbon and carbon-heteroatom bonds. A characteristic feature of this process is the predominant formation of branched products.[11] The introduction of prochiral nucleophiles to Ir-catalyzed allylic substitutions would provide an effective and reliable method for the synthesis of the products containing vicinal stereocenters. Indeed, the diastereo- and enantioselective reactions with carbonyl heterocyclic compounds, aldehydes or β-ketoesters as nucleophiles in

Scheme 1. Stereodivergent Synthesis *via* Bimetallic Catalysis

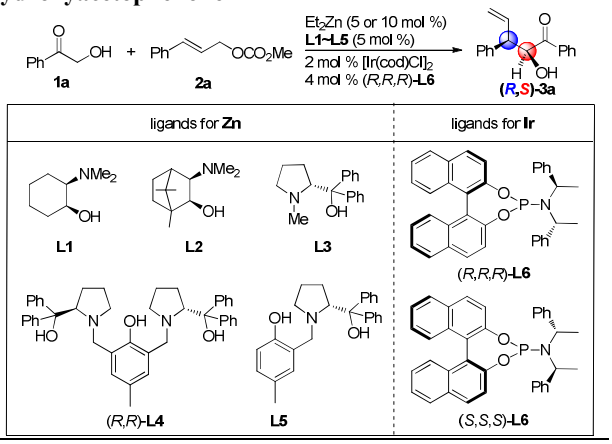


this area have been achieved recently through elegant contributions from the groups of Hartwig, Carreira and Stoltz.[6,12] However, the direct use of unprotected α-hydroxyketones as nucleophiles in Ir-catalyzed allylic substitution remains challenging (Scheme 1b).[13-14] It is worth noting that α-hydroxyketone donors are particularly interesting because of the important biological activity of the polyoxygenated products.[15-16] However, these are troublesome nucleophiles due to their multiple nucleophilic sites and the undefined geometry of the corresponding unstabilized enolate. Herein, we describe an enantio- and diastereodivergent synthesis for the α-allylation of unprotected α-hydroxyketones, a procedure greatly desired from an atom economy and synthetic efficiency perspective.[17]

In continuation of our previous work concerning dual catalysis for asymmetric allylic substitutions in which transition-metal catalysis and enamine catalysis were combined,[18] we envisioned that a dual catalyst system consisting of a combination of a chiral zinc complex[16,19] and a chiral iridium complex[20] would provide an efficient strategy for the enantio- and diastereodivergent α-allylations of unprotected α-hydroxyketones (Scheme 1b). The potential advantages of this strategy are as follows: (i) A five-membered ring containing zinc enolate **II-1** will be formed *via* the coordination of the zinc atom with the two oxygen atoms of the carbonyl and the hydroxyl groups. The formation of **II-1** may improve the nucleophilicity of the carbon atom; (ii) Zinc enolate

II-1 has a defined *Z*-configuration, which may provide a general approach to acyclic diastereocontrol; (iii) The cooperative use of a chiral zinc complex and a chiral iridium complex may simultaneously activate the α-hydroxyketone and the allyl and allow for the control of the two stereocenters. This will increase the possibility of an enantio- and diastereodivergent α-allylation of α-hydroxyketones.[7]

Table 1. Optimization of the α-Allylation of α-Hydroxyacetophenone[a]



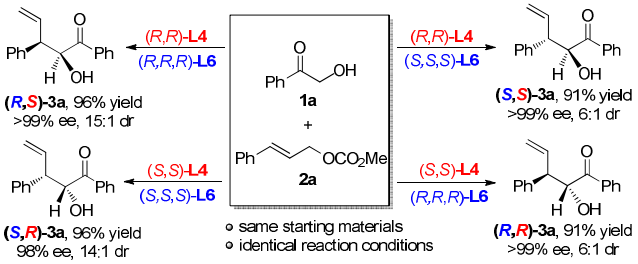
entry	Zn/L	L	additive	yield (%)[b]	dr[c]	ee (%)[d]
1	–	–	–	nr	–	–
2	1:1	**L1**	–	38	1:1	79/81
3	1:1	**L2**	–	48	1:1	89/89
4	1:1	**L3**	–	42	1:1	87/70
5	2:1	**L4**	–	63	3:1	93/90
6[e]	2:1	**L4**	EC	71	3:1	96
7[e]	2:1	**L4**	Ph_3PO	65	3:1	94
8[e]	2:1	**L4**	Ph_3PS	74	3:1	94
9[f]	2:1	**L4**	4Å MS	94	6:1	97
10[g]	2:1	**L4**	4Å MS	97	8:1	98
11[g]	1:1	**L4**	4Å MS	97	13:1	99
12[g,h]	1:1.2	**L4**	4Å MS	96	15:1	>99
13[g,i]	1:1.5	**L4**	4Å MS	96	16:1	>99
14[g]	1:1	**L5**	4Å MS	93	1:1	87/52

[a]Reaction conditions: **1a** (0.30 mmol, 1.2 equiv), **2a** (0.25 mmol, 1.0 equiv), Et_2Zn (5 or 10 mol %), **L1**–**L5** (5 mol %), $[Ir(cod)Cl]_2$ (2 mol %), (*R,R,R*)–**L6** (4 mol %), rt, 12 h. [b]Isolated yield. nr = no reaction. [c]Ratio of dr determined by ^1H NMR integration. [d]Determined by HPLC analysis using an OD-H column. [e]20 mol % additives. [f]50 mg 4Å MS. [g]100 mg 4Å MS. [h]Et_2Zn (5 mol %), **L4** (6 mol %). [i]Et_2Zn (5 mol %), **L4** (7.5 mol %). EC = ethylene carbonate.

The investigation began using α-hydroxyacetophenone (**1a**) and cinnamyl methyl carbonate (**2a**) as model substrates for the allylic substitution (Table 1). The asymmetric reaction was first attempted using a bimetallic catalyst system consisting of a Et_2Zn complex modified with appropriate amino alcohol ligands (**L1**–**L5**)[19] and an iridium complex derived from phosphoramidites [(*R,R,R*)–**L6**].[20] In the absence of the Zn catalyst, none of the desired product α-hydroxyl-γ,δ-unsaturated ketone (**3a**) was obtained (entry 1). This situation could be reversed via the addition of a Zn catalyst, giving the desired product **3a** in moderate yields (entries 2–5). After examination of different ligands (**L1**–**L4**), the Trost ligand–ProPhenol (**L4**) was shown to give superior results compared to all others tested. The Zn–ProPhenol complex was therefore chosen as the optimal Zn catalyst.[19c] Compared to the mono-catalyst consisting of only an Ir complex, the addition of the Zn catalyst greatly improved the reactivity and selectivity of the α-hydroxyketone. The efficiency of the Zn–ProPhenol catalyst could be further improved by the addition of a weak coordinating agent that is able to displace the product.[16b,c,e-g,21] Indeed, the addition of a small amount of weak coordinating agent such as ethylene carbonate, $Ph_3P{=}O$ or $Ph_3P{=}S$, accelerated the asymmetric transformation under otherwise identical conditions (entries 6–8). The addition of 4Å MS further promoted reaction activity, giving **3a** in high yields with good diastereo- and enantioselectivities (entries 9–10). Subsequent optimization studies showed that the ratio of Et_2Zn and **L4** could be reduced to 1:1.2 to give **3a** in 96% yield, 15:1 dr, and >99% ee (entries 11–13). The unusual Zn/**L4** ratio prompted us to synthesize and apply the ligand **L5** to the catalysis. However, this led to poor catalytic performance (entry 14). Although we are unable to clarify the underlying reason for the outstanding catalytic performance of the Trost ligand–ProPhenol, the unique geometry of the chiral semi-crown backbone seems to be critically important for the reactivity and stereocontrol of the catalysis.

With the feasibility of a chemo- and stereoselective process for the α-allylation of α-hydroxyacetophenone established, we then speculated if the bimetallic catalyst system could furnish product **3a** with full control over the absolute and relative configuration of its two stereocenters. Under the optimized reaction conditions (Table 1, entry 12), the reaction of **1a** and **2a** afforded product (*R,S*)–**3a** in 96% yield, 15:1 dr, and >99% ee when catalyzed with the (*R,R*)–**L4**/(*R,R,R*)–**L6** combination. Significantly, the reaction allowed for the synthesis of (*S,S*)–**3a** in 91% yield, 6:1 dr, and >99% ee when catalyzed by the (*R,R*)–**L4**/(*S,S,S*)–**L6** combination (Scheme 2). The switch in the sense of diastereoselectivity suggested that the two chiral metal catalysts were able to almost independently control the configuration of the two stereocenters. From the same set of starting materials and under identical reaction conditions, the remaining two stereoisomers (*S,R*)–**3a** and (*R,R*)–**3a** were prepared in high yields and good enantio- and diastereoselectivities (Scheme 2).

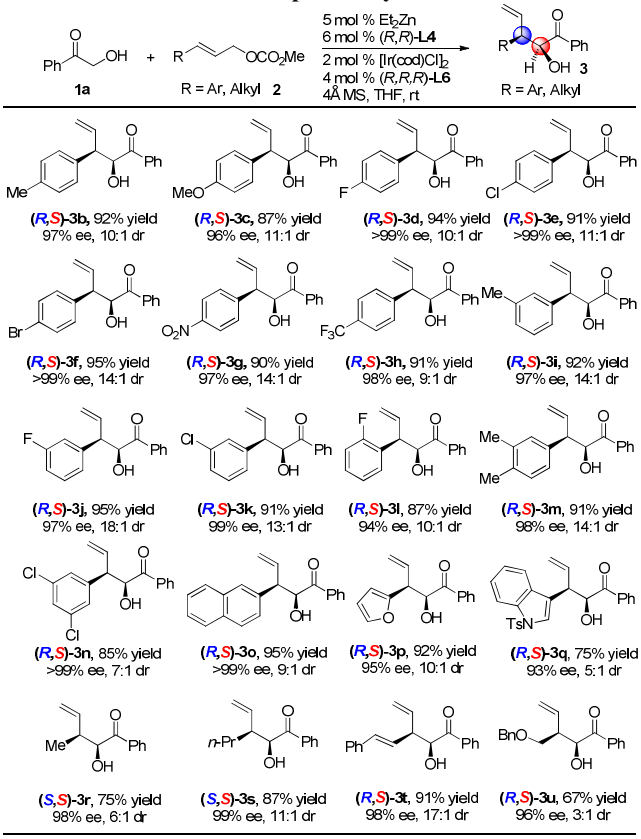
Scheme 2. Synthesis of All Four Stereoisomers of 3a



A number of allylic esters were examined (Table 2). Allylic esters bearing either electron-donating or electron-withdrawing groups at the *ortho*-, *meta*-, or *para*-position of the arene functionality participated in this reaction to give the desired products (**3b**–**3n**) in high yields and with excellent stereoselectivities (7:1 to 18:1 dr, 94–>99% ee). Furthermore, the reactions of naphthyl- and heteroaryl-substituted allyl carbonates were successfully carried out to give their respective products in good yields and with excellent enantioselectivities (**3o**–**3q**). Commom substituents such as alkyl, styrenyl and ether groups also gave good results (**3r**–**3u**).

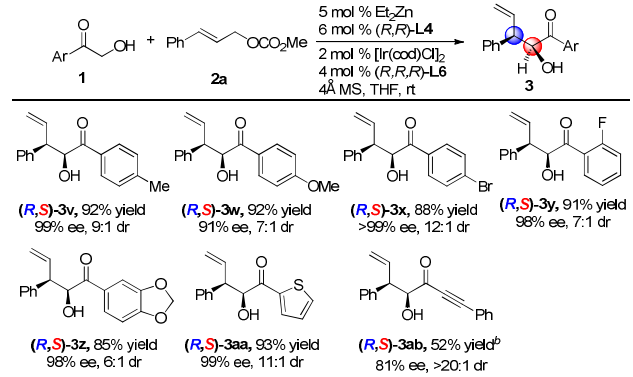
The scope of a series of α-hydroxyketones was next investigated (Table 3). α-Hydroxyacetophenones substituted with Me, OMe, Br, F, and 3,4-methylenedioxy groups gave the desired products (**3v**–**3z**) in high yields and with excellent stereoselectivities (6:1 to 12:1 dr, 90–>99% ee). An α-hydroxyketone incorporating a heteroarene also proved to be a good substrate for this reaction, affording product **3aa** in high yield and excellent enantioselectivity. Additionally, alkyne-substituted hydroxyketone was smoothly used as a nucleophile in this reaction, providing the desired product **3ab** in moderate yield and high ee.

Table 2. The Substrate Scope of Allylic Carbonates[a]



[a]Reaction conditions, please see Table 1, entry 12.

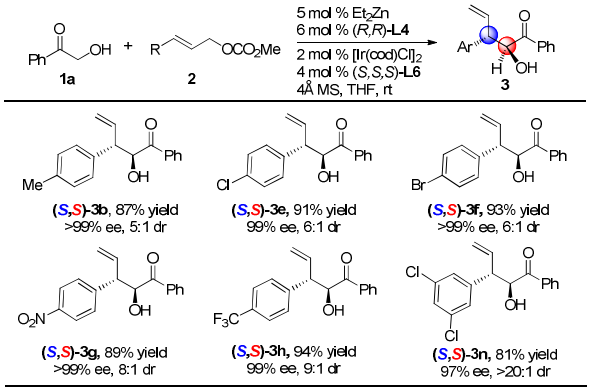
Table 3. The Substrate Scope of α-Hydroxyketones[a]



[a]Reaction conditions, please see Table 1, entry 12. [b]at 80 °C.

To evaluate the practicality of the diastereodivergent synthesis, we performed the reactions of **1a** with different allylic carbonates using a combination of (*R,R*)–**L4**/(*S,S,S*)–**L6** (Table 4). Cinnamyl carbonates substituted with arenes bearing methyl, halogen, and other electron-withdrawing substituents reacted smoothly to give the corresponding products in good yields and with excellent enantioselectivities, although most of the dr values were slightly lower than those obtained with the combination of (*R,R*)–**L4**/(*R,R,R*)–**L6**.

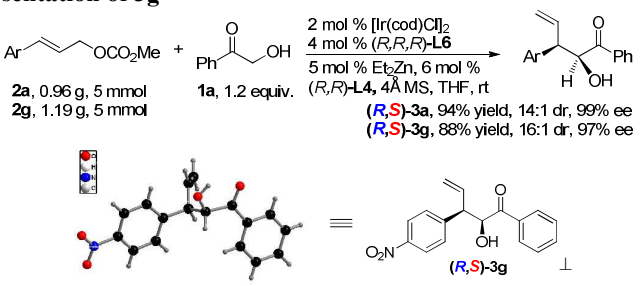
Table 4. Representative Examples of Stereodivergence[a]



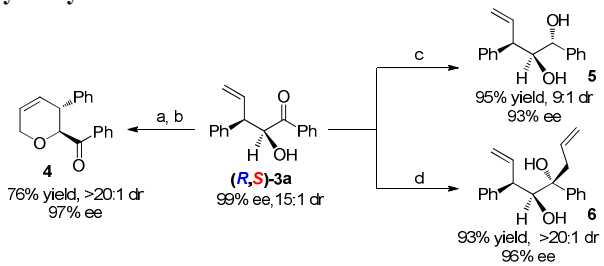
[a]Reaction conditions, please see Table 1, entry 12 with (*S,S,S*)–**L6** instead of (*R,R,R*)–**L6**.

To confirm the scalability of the present method, we performed a gram-scale synthesis of (*R,S*)–**3a** and (*R,S*)–**3g** using the standard reaction conditions and comparable results were obtained (Scheme 3). Furthermore, the absolute configuration of (*R,S*)–**3g** was determined by single-crystal X-ray analysis.

Scheme 3. Gram-scale Experiments and ORTEP Representation of 3g



Scheme 4. Synthetic Transformation of the Allylated α-Hydroxyketone[a]



[a]Reaction conditions: (a) allyl iodide, DMF, Cs_2CO_3, rt, 6 h. (b) Grubbs–Hoveyda catalyst, DCM, 40 °C, 12 h. (c) $NaBH_4$, EtOH, 0 °C, 2 h. (d) potassium allyltrifluoroborate, $CeCl_3$, THF, 50 °C, 6 h.

Subsequently, synthetic transformations of the product (*R,S*)–**3a** were conducted. As shown in Scheme 4, chiral dihydropyran **4** could be easily obtained from (*R,S*)–**3a** via allylic substitution and ring-closing metathesis using a Grubbs–Hoveyda second generation catalyst. Reduction of (*R,S*)–**3a** with $NaBH_4$ furnished compound **5** in 95% yield and 93% ee.[22] The allylation of (*R,S*)–**3a** with potassium allyltrifluoroborate led to the allylated polyoxygenated product **6** in 93% yield and 96% ee.[22]

In summary, we have developed a new bimetallic catalysis

strategy for a one-step and stereodivergent α-allylation of unprotected α-hydroxyketones by using a chiral iridium complex derived from phosphoramidites and a chiral Zn−ProPhenol complex in the absence of any additional bases. A range of chiral α-hydroxyl-γ,δ-unsaturated ketones containing vicinal stereocenters were produced in good yields and with excellent stereoselectivities. More significantly, the pairwise combination of chiral metal catalysts allows for complete control over the absolute and relative configuration of all possible product stereoisomers from the same set of starting materials under identical reaction conditions. We envisage that this bimetallic catalyst strategy will offer new opportunities for full stereodivergent access to difficult asymmetric transformations.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

wanbin@sjtu.edu.cn.

Author Contributions

§ These authors contributed equally.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the NSFC (Nos. 21232004 and 21472123) and Science and Technology Commission of Shanghai Municipality (Nos. 14XD1402300 and 15Z111220016) for financial support.

REFERENCES

(1) Jozwiak, K.; Lough, W. J.; Wainer, I. W. Eds. *Drug Stereochemistry: Analytical Methods and Pharmacology*, 3rd ed.; Informa, 2012.

(2) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds. *Comprehensive Asymmetric Catalysis*: *Vol. I−III, Suppl. I-II*; Springer: New York, 1999.

(3) (a) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934. (b) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 20628.

(4) (a) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (b) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3779. (c) Luparia, M.; Oliveira, M. T.; Audisio, D.; Frébault, F.; Goddard, R.; Maulide, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 12631.

(5) (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (b) Chi, Y.; Scroggins, S. T.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6322. (c) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349. (d) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. *Nature* **2016**, *532*, 353.

(6) (a) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (b) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3020. (c) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363. (d) Næsborg, L.; Halskov, K. S.; Tur, F.; Mønsted, S. M. N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 10193.

(7) For perspectives on stereodivergent dual catalysis, see: (a) Schindler, C. S.; Jacobsen, E. N. *Science* **2013**, *340*, 1052. (b) Oliveira, M. T.; Luparia, M.; Audisio, D.; Maulide, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 13149.

(8) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928.

(9) (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) Zhou, Q.-L. Ed. *Privileged Chiral Ligands and Catalysts*; Wiley-VCH, 2011.

(10) (a) Ojima, I. Ed. *Catalytic Asymmetric Synthesis*, 3rd ed.; Wiley-VCH: New York, 2009. (b) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books, Sausalito, CA, 2010.

(11) For selected reviews, see: (a) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (d) Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169. (e) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2012**, *38*, 155. (f) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, 3179. (g) Helmchen, G. *In Molecular Catalysts*; Gade, L. H.; Hofmann, P. Eds.; Wiley-VCH: Weinheim, 2014; pp 235−254.

(12) (a) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2068. (b) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626. (c) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 17298. (d) Chen, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 377. (e) Chen, W.; Chen, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 15825. For the intramolecular reaction, see: (f) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418.

(13) (a) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.*, **2004**, *126*, 8642. (b) Jiang, X.; Chen, W.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 5819.

(14) For examples of Pd-catalyzed asymmetric allylic alkylation of α-hydroxyketones, see: (a) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2008**, *130*, 11852.

(15) (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (b) Tiaden, A.; Spirig, T.; Hilbi, H. *Trends Microbiol.* **2010**, *18*, 288.

(16) The use of hydroxyketones as a donor in asymmetric Aldol and Mannich-type reactions, see: (a) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003. (e) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (f) Trost, B. M.; Malhotra, S.; Fried, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 1674. (g) Trost, B. M.; Michaelis, D. J.; Truica, M. I. *Org. Lett.* **2013**, *15*, 4516.

(17) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (c) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193.

(18) (a) Zhao, X.; Liu, D.; Xie, F.; Liu, Y.; Zhang, W. *Org. Biomol. Chem.* **2011**, *9*, 1871. (b) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. *J. Am. Chem. Soc.* **2011**, *133*, 19354. (c) Huo, X.; Quan, M.; Yang, G.; Zhao, X.; Liu, D.; Liu, Y.; Zhang, W. *Org. Lett.* **2014**, *16*, 1570. (d) Huo, X.; Yang, G.; Liu, D.; Liu, Y.; Gridnev, I. D.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 6776. For reviews on combined metal and organic catalysis, see: (e) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (f) Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337. (g) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44*, 7929.

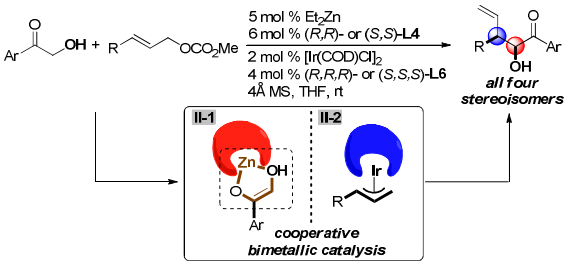
(19) For selected reviews, see: (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (b) Łowicki, D.; Baś, S.; Mlynarski, J. *Tetrahedron* **2015**, *71*, 1339. (c) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688.

(20) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.

(21) Several bidentate coordinating agents were also explored. For more details please see the Supporting Information.

(22) The absolute configurations of **5** and **6** were determined by single-crystal X-ray analysis. For more details please see the Supporting Information.

An Ir/Zn dual catalysis has been developed for the enantio- and diastereodivergent α-allylation of unprotected α-hydroxyketones under mild conditions, in the absence of any additional base. The cooperative action of a chiral iridium complex derived from phosphoramidites and a chiral Zn-ProPhenol complex is most likely responsible for its high reactivity, excellent enantioselectivity (up to >99% ee), and good diastereoselectivity (up to >20:1 dr). All four product stereoisomers could be prepared from the same set of starting materials and under identical conditions by simple selection of appropriate catalyst combinations.



37 examples, up to 96% yield, >99% ee, and >20:1 dr