Communication

Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis

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Stereodivergent Allylation of Azaaryl Acetamides and Acetates by Synergistic Iridium and Copper Catalysis

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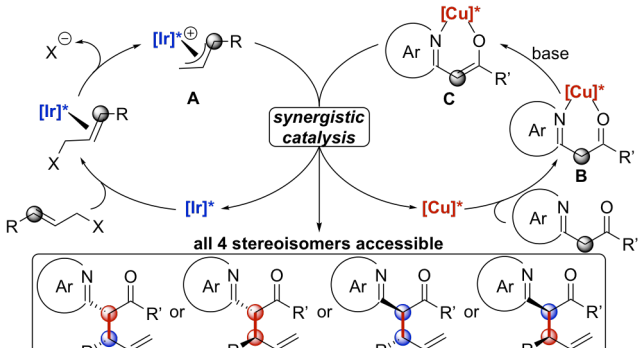
Supporting Information Placeholder

ABSTRACT: We report stereodivergent allylic substitution reactions of allylic esters with prochiral enolates derived from azaaryl acetamides and acetates to form products from addition of the enolates at the most substituted carbon of an allyl moiety with two catalysts, a chiral metallacyclic iridium complex and a chiral bisphosphine-ligated copper(I) complex, which individually control the configuration of the electrophilic and nucleophilic carbon atoms, respectively. By simple permutations of enantiomers of the two catalysts, all four stereoisomers of products containing two stereogenic centers were synthesized individually with high diastereoselectivity and enantioselectivity. A variety of azaaryl acetamides and acetates bearing pyridyl, benzothiazolyl, benzoxazolyl, pyrazinyl, quinolinyl and isoquinolinyl moieties were all found to be suitable for this transformation.

Chiral molecules bearing nitrogen-containing heteroaromatic rings (azaarenes) are ubiquitous in natural products, pharmaceuticals and agrochemicals. The configuration of the stereogenic centers in these molecules typically alters their physiological properties. Therefore, a synthetic method would be valuable that provides access to all possible stereoisomers of a given azaaryl compound with multiple adjacent stereocenters from the same set of starting materials under almost identical conditions.[1] This proposed method would enable the rapid synthesis of all stereoisomers of chiral azaaryl compounds for testing of biological activity and for studies on structure-activity relationships (SAR).[2] However, reported stereodivergent reactions involving substrates containing azaarenes are limited,[3] and the basic property of an azaaryl motif has not been used to facilitate stereodivergent reactions.[4]

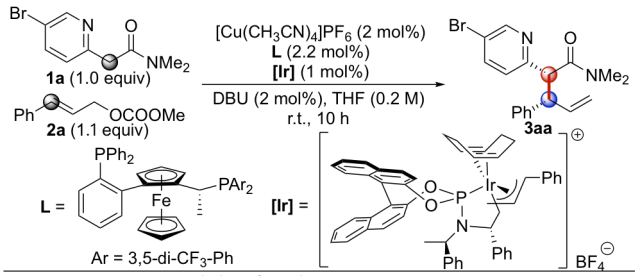
Our group has previously reported metallacyclic iridium catalysts[5] that govern the geometry, facial selectivity, and regioselectivity of the allyl moiety (Scheme 1, **A**) in asymmetric allylic substitutions.[6] Recently we developed stereodivergent allylations of aryl acetic acid esters catalyzed by these Ir catalysts and a chiral Lewis base.[3h] This work has led us to consider whether our Ir catalysts would be compatible with chiral Lewis-acid catalysts that could bind Lewis-basic nitrogen atoms on azaarenes and subsequently catalyze stereodivergent allylations of azaaryl compounds.

Scheme 1. Proposed Mechanism for Synergistic Catalysis.



Chiral bisphosphine-ligated copper(I) complexes are known to act as Lewis acids that catalyze asymmetric functionalizations of well-designed amides through two-point binding with the amides.[4c,7] We envisioned that the Cu(I) complexes could bind azaaryl acetamides and acetates in a similar manner. The C=N moiety embedded at a suitable position in azaaryl rings and the nearby carbonyl groups in azaaryl acetamides and acetates would serve as the basic sites for the bidentate coordination of the Lewis acid (Scheme 1, **B**). After deprotonation, the resulting Cu(I) enolate (Scheme 1, **C**) would be formed with well-defined geometry and would react with electrophilic intermediate **A** with high facial selectivity, affording the allylated azaaryl products with high regio-, diastereo- and enantioselectivity.[8] The Ir catalyst and the Cu(I) catalyst would dictate the configurations of two adjacent stereocenters in the product generated from the electrophile and the nucleophile, respectively.[9] Therefore, by simple permutations of enantiomers of the two catalysts, all four possible stereoisomers of the product could be accessible (Scheme 1).[1]

Table 1. Evaluation of Reaction Conditions for the Allylation of 1a



entry	variations from the standard condition	dr[a]	ee/%[b]	yield/%[c]
1	none	>20:1	>99	97 (97)
2	no $[Cu(CH_3CN)_4]PF_6$ or **L**	1:1.8	n.d.	14
3	no **L**	1.4:1	n.d.	91
4	no **[Ir]**			<1
5	no DBU			<1
6	*ent*-**[Ir]** instead of **[Ir]**	1:>20	>99	88 (84)

[a]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Determined by chiral SFC analysis of the major isomer. [c]Combined yield of two diastereomers of the product. Determined by ^{1}H NMR analysis with mesitylene as an internal standard. The yield within parentheses is that of the major diastereomer isolated.

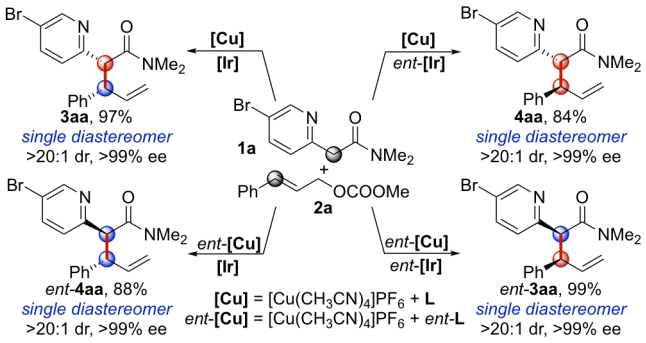
Herein we report stereodivergent allylic substitutions with azaaryl acetamides and acetates catalyzed synergistically by a metallacyclic Ir complex and a chiral Cu (I) complex. Variation of the combination of enantiomers of the catalysts allows access to all four possible stereoisomers of the allylation products from the same set of starting materials under otherwise identical conditions. Various azaaryl acetamides and acetates containing pyridyl, benzoxazolyl, benzothiazolyl, pyrazinyl, quinolinyl and isoquinolinyl moieties were all suitable for this transformation, delivering the products with high diastereoselectivity and enantioselectivity.

We began our studies on the stereodivergent allylic substitutions with azaaryl acetamides and acetates by examining the reaction between amide **1a** (1.0 equiv) and carbonate **1b** (1.1 equiv) with $[Cu(CH_3CN)_4]PF_6$ (5 mol%), metallacyclic iridium catalyst **[Ir]** shown in Table 1 (2 mol%), DBU (5 mol%) as catalytic base, and a series of chiral bisphosphine ligands (5.5 mol%, Table S1). We found that a Cu(I) complex ligated by Walphos derivative **L** is an effective Lewis acid for the proposed synergistic catalysis, delivering product **3aa** in 94% yield with >20:1 dr. Reactions conducted with copper complexes ligated by chiral bisphosphines derived from BINAP, Garphos, Segphos and Josiphos afforded **3aa** in similar yields but with lower diastereoselectivity (<7:1 dr). Further studies on the loading of the two catalysts revealed that reaction conducted with 2 mol% of the Cu complex and 1 mol% of **[Ir]** gave **3aa** in 97% yield (isolated as a single diastereomer) with >20:1 dr and >99% ee (Table 1, entry 1). A gram-scale synthesis of **3aa** was conducted with 1 mol% of the Cu complex and 0.5 mol% of **[Ir]**. The product was obtained in 96% yield (1.04 g) with >20:1 dr and >99% ee (see SI for details).

To understand the role of individual reaction components in this reaction, a set of control experiments were conducted. The reaction conducted with the iridium catalyst **[Ir]** without $[Cu(CH_3CN)_4]PF_6$ or **L** gave **3aa** in a low yield of 14% with low diastereoselectivity (1:1.8 dr), slightly favoring the formation of the diastereomer of **3aa** (entry 2). This result and the result in entry 1 demonstrate that the configuration of the nucleophilic carbon in the product results from catalyst control, rather than substrate control. The reaction occurred smoothly when catalyzed by **[Ir]** and $[Cu(CH_3CN)_4]PF_6$ as the Lewis-acid catalyst without **L** (91% yield, entry 3). However, a low diastereoselectivity of 1.4:1 dr was observed, indicating that the facial selectivity of the unligated Cu(I) enolate in the allylation reaction is poor. No product was formed in the absence of **[Ir]** (entry 4). A catalytic amount of DBU was necessary to initiate the reaction (entry 5), presumably by deprotonating **1a** to form the corresponding Cu(I) enolate. The methyl carbonate anion generated from oxidative addition of **2a** or the methoxide generated from decarboxylation of the methyl carbonate anion would likely act as a base for deprotonation of the substrate in subsequent turnovers.

To test the role of iridium in the stereodivergent allylation, we conducted the reaction with the enantiomer of **[Ir]** instead of **[Ir]**, while keeping the configuration of the Cu(I) complex constant. The diastereomer of **3aa** was obtained

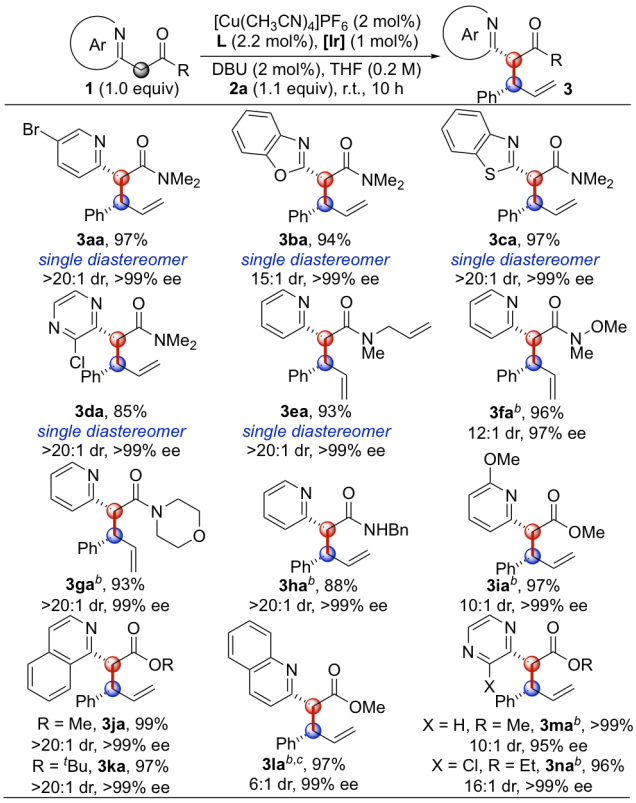
Scheme 2. Synthesis of All Four Stereoisomers of 3aa.



from this reaction, instead of **3aa**, with excellent diastereoselectivity and enantioselectivity (entry 6, 84% yield, isolated as a single diastereomer, 1:>20 dr, >99% ee). This result indicates that the Ir complex and the Cu(I) complex exert nearly complete and independent control over the configurations of stereocenters arising from the allyl electrophile and the enolate nucleophile, respectively. The stereodivergence of this allylation method was further evaluated by treating **1a** and **2a** with four different combinations of enantiomers of the two catalysts under otherwise identical conditions (Scheme 2). All four stereoisomers of **3aa** were formed individually from these reactions and separated as a single diastereomer in high yields (>80%) with excellent diastereo- and enantioselectivity (>20:1 dr, >99% ee).

The scope of azaaryl acetamides and acetates that underwent the stereodivergent allylic substitutions is summarized in Table 2. *N,N*-Dimethyl acetamides that bear pyridyl (**1a**), benzoxazolyl (**1b**), benzothiazolyl (**1c**) and pyrazinyl (**1d**) moieties on the α carbon were all suitable for this transformation, affording products **3aa–3da** in ≥85% yield (isolated as a single diastereomer) with ≥15:1 dr and >99% ee. In addition to *N,N*-dimethyl amides, pyridyl

Table 2. Scope of Azaaryl Acetamides and Acetates for the Allylation[a]

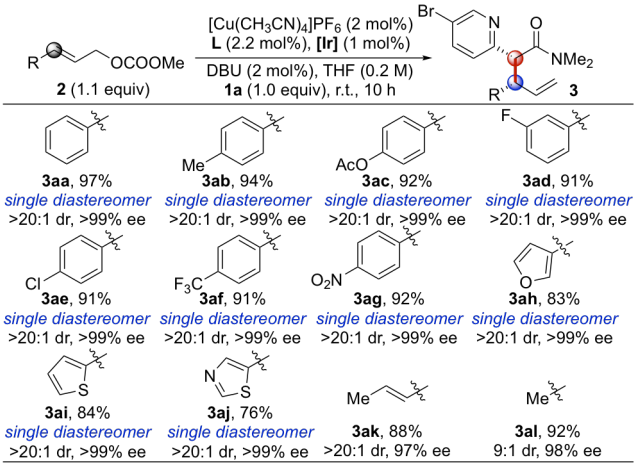


[a]**3aa-3ea** were isolated as a single diastereomer. The yields for other products were reported as the combined yields of two diastereomers isolated. [b][Cu(CH$_3$CN)$_4$]PF$_6$ (5 mol%), **L** (5.5 mol%), **[Ir]** (2 mol%), DBU (5 mol%). [c]The ee value was determined after further transformation of the product. See SI for details.

acetamides generated from *N*-allylmethyl amine (**1e**), *N,O*-dimethylhydroxyl amine (**1f**) and morpholine (**1g**) reacted to form products **3ea**–**3ga** in ≥93% yield with ≥12:1 dr and ≥97% ee. A secondary *N*-benzyl pyridyl acetamide, bearing an amide N–H bond, reacted selectively at the α position over the nitrogen of the amide (**3ha**, 88% yield, >20:1 dr, >99% ee). In some cases (**3fa**–**3ha**), the reactions were conducted with 5 mol% of the Cu complex and 2 mol% of **[Ir]** instead of 2 mol% and 1 mol%, respectively, to obtain the products with high diastereoselectivity.

Various azaaryl acetates bearing pyridyl (**1i**), isoquinolinyl (**1j**, **1k**), quinolinyl (**1l**) and pyrazinyl (**1m**, **1n**) moieties were tested for this allylation reaction. Pyridyl acetate **1i** reacted smoothly to afford product **3ia** in 97% yield with 10:1 dr and >99% ee. The size of the group on the oxygen of the ester had little impact on the allylation reaction; methyl ester **1j** and *tert*-butyl ester **1k** reacted similarly to give product **3ja** and **3ka**, respectively, in almost quantitative yield (≥97%) with excellent diastereo- and enantioselectivity (>20:1 dr, >99% ee). Quinolinyl acetate **1l** reacted to give allylation product **3la** in 97% yield with 6:1 dr and 99% ee.[10] Acetates bearing pyrazinyl (**1m**, **1n**) moieties containing two Lewis basic nitrogen atoms in the azaarene also were suitable for this transformation, giving the allylation products in high yield (≥96%) with ≥10:1 dr and ≥95% ee.

Table 3. Scope of Allylic Carbonates for the Allylation[a]

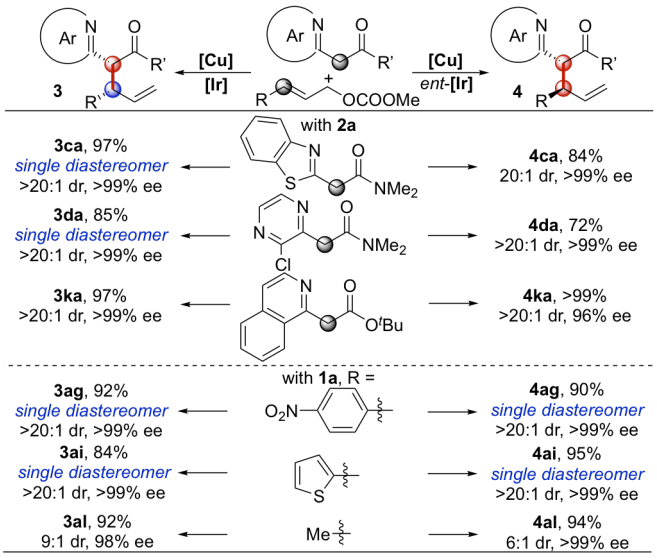


[a]**3aa-3aj** were isolated as a single diastereomer. The yields for others were reported as the combined yields of two diastere-

The scope of allyl methyl carbonates that underwent the stereodivergent allylic substitution reactions is summarized in Table 3. Electron-neutral (**2b**), electron-donating (**2c**) and electron-withdrawing (**2d**–**2g**) functional groups on the cinnamyl aryl rings were all tolerated by the allylation reaction, and the corresponding products (**3ab**–**3ag**) were obtained in excellent yield (>90%, isolated as a single diastereomer) with >20:1 dr and >99% ee. Carbonate **2c** bearing a base-sensitive acetoxy group on the phenyl ring reacted cleanly to afford **3ac**, highlighting the mildness of these reaction conditions.

This reaction also occurred with carbonates that bear heteroaryl, alkenyl and alkyl substituents. Carbonates that contain furyl (**2h**), thienyl (**2i**) and thiazolyl (**2j**) substituents underwent the allylation reaction to give the products (**3ah**–**3aj**) in >75% yield (isolated as a single diastereomer) with >20:1 dr and >99% ee. Methyl sorbyl carbonate (**2k**) reacted to afford product **3ak** in 88% yield with >20:1 dr and 97% ee. Even simple crotyl carbonate (**2l**) reacted similarly to give the allylation product in 92% yield with

Table 4. Examples of Stereodivergence



9:1 dr and 98% ee.

To demonstrate the stereodivergence of this allylation reaction further, the diastereomers of **3ca**, **3da**, **3ka**, **3ag**, **3ai** and **3al** were prepared by conducting the reactions with the corresponding azaaryl nucleophiles and the carbonates in the presence of *ent*-**[Ir]** instead of **[Ir]** under otherwise identical conditions (Table 4). The corresponding products (**4ca**, **4da**, **4ka**, **4ag**, **4ai**, **4al**) were obtained from these reactions in yields, diastereo- and enantioselectivity that are comparable to those of the reactions that form their diastereomers.

In summary, we have developed a combination of catalysts that enable stereodivergent allylic substitution reactions with azaaryl acetamides and acetates. This combination of catalysts comprises a chiral metallacyclic iridium complex and a chiral bisphosphine-ligated copper(I) complex. The phosphoramidite binds Ir tightly through a stable Ir–C bond, which prevents potential crossover of two ligands on two metal centers. The copper(I) complex acts as a Lewis acid to activate the azaaryl carboxylic acid derivatives by coordinating to the imine moieties (C=N) embedded in the azaaryl rings and the suitably positioned carbonyl groups, and this binding mode of the chiral complex controls the geometry and facial selectivity of the Cu(I) enolates in the allylation reactions. Azaaryl substrates that bear pyridyl, benzoxazolyl, benzothiazolyl, pyrazinyl, quinolinyl and isoquinolinyl moieties all underwent this reaction, delivering the products containing two adjacent tertiary stereocenters in high yields with excellent diastereo- and enantioselectivity. Starting from the same set of substrates, simple variation of the enantiomers of the two catalysts allow the synthesis of all four possible stereoisomers of the products individually. Studies to understand the origin of stereoselectivity of the Cu(I) enolates in the allylation reactions are ongoing in our laboratories.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectra (PDF)
Crystallographic data for **3ca** (CIF)
Crystallographic data for **4ca** (CIF)

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REFERENCES

(1) Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2017,** *139*, 5627.

(2) (a) *Pharmaceutical Process Development: Current Chemical and Engineering Challenges*; Blacker, A. J., Williams, M. T., Eds; Royal Society of Chemistry: Cambridge, 2011; (b) *Drug Stereochemistry: Analytical Methods and Pharmacology* (3rd ed.); Jozwiak, K.; Lough, W. J.; Wainer, I. W., Eds; Informa: London, 2012.

(3) (a) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013,** *340*, 1065; (b) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014,** *136*, 3020; (c) Næsborg, L.; Halskov, K. S.; Tur, F.; Mønsted, S. M. N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015,** *54*, 10193; (d) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2015,** *54*, 14363; (e) Huo, X.; He, R.; Zhang, X.; Zhang, W. *J. Am. Chem. Soc.* **2016,** *138*, 11093; (f) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2017,** *139*, 10641; (g) He, R.; Liu, P.; Huo, X.; Zhang, W. *Org. Lett.* **2017,** *19*, 5513; (h) Jiang, X.; Beiger, J. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2017,** *139*, 87; (i) Kassem, S.; Lee, A. T. L.; Leigh, D. A.; Marcos, V.; Palmer, L. I.; Pisano, S. *Nature* **2017**, *549*, 374.

(4) For selected recent reviews on asymmetric reactions (but not stereodivergent) of azaarenes catalyzed by Lewis acids: (a) Best, D.; Lam, H. W. *J. Org. Chem.* **2014,** *79*, 831; (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2015,** *115*, 9922; (c) Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2016,** *22*, 15192. For selected recent pulications on asymmetric functionalizations (but not stereodivergent) of azaarenes: (d) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011,** *133*, 12439; (e) Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K. *J. Am. Chem. Soc.* **2010,** *132*, 891; (f) Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2016,** *138*, 3282; (g) Jumde, R. P.; Lanza, F.; Veenstra, M. J.; Harutyunyan, S. R. *Science* **2016,** *352*, 433; (h) Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2016,** *22*, 15192; (i) Smith, J. J.; Best, D.; Lam, H. W. *Chem. Commun.* **2016,** *52*, 3770; (j) Bastida, I.; Segundo, M. S.; López, R.; Palomo, C. *Chem. Eur. J.* **2017,** *23*, 13332; (k) Ma, J.; Rosales, A. R.; Huang, X.; Harms, K.; Riedel, R.; Wiest, O.; Meggers, E. *J. Am. Chem. Soc.* **2017**, *139*, 17245.

(5) For original discoveries: (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002,** *124*, 15164; (b) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003,** *125*, 14272. For mechanistic studies: (c) Madrahimov, S. T.; Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009,** *131*, 7228; (d) Madrahimov, S. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012,** *134*, 8136; (e) Chen, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015,** *137*, 13972; (f) Madrahimov, S. T.; Li, Q.; Sharma, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015,** *137*, 14968. For our recent publications: (g) Chen, M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2016,** *55*, 11651; (h) Jiang, X.; Chen, W.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2016,** *55*, 5819; (i) Jiang, X.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2017,** *56*, 8887.

(6) For selected recent Ir-catalyzed asymmetric allylation reactions: (a) Hamilton, J. Y.; Rössler, S. L.; Carreira, E. M. *J. Am. Chem. Soc.* **2017,** *139*, 8082; (b) Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. *Org. Lett.* **2017,** *19*, 1527; (c) Huang, L.; Cai, Y.; Zheng, C.; Dai, L.-X.; You, S.-L. *Angew. Chem. Int. Ed.* **2017,** *56*, 10545; (d) Liu, X.-J.; You, S.-L. *Angew. Chem. Int. Ed.* **2017,** *56*, 4002; (e) Sandmeier, T.; Krautwald, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2017,** *56*, 11515; (f) Schafroth, M. A.; Rummelt, S. M.; Sarlah, D.; Carreira, E. M. *Org. Lett.* **2017,** *19*, 3235; (g) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2017,** *56*, 11545; (h) Wang, Y.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed.* **2017,** *56*, 15093.

(7) For selected recent publications: (a) Kumagai, N.; Kanai, M.; Sasai, H. *ACS Catal.* **2016,** *6*, 4699; (b) Liu, Z.; Takeuchi, T.; Pluta, R.; Arteaga, F.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2017,** *19*, 710; (c) Sun, B.; Balaji, P. V.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.*

2017, *139*, 8295; (d) Zhang, H.-J.; Shi, C.-Y.; Zhong, F.; Yin, L. *J. Am. Chem. Soc.* **2017,** *139*, 2196.

(8) For recent reports on Pd-catalyzed asymmetric allylations of chiral Cu enolates: (a) Huo, X.; He, R.; Fu, J.; Zhang, J.; Yang, G.; Zhang, W. *J. Am. Chem. Soc.* **2017,** *139*, 9819; (b) Saito, A.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2017,** *56*, 5551; (c) Wei, L.; Xu, S.-M.; Zhu, Q.; Che, C.; Wang, C.-J. *Angew. Chem. Int. Ed.* **2017,** *56*, 12312.

(9) For selected recent reviews on dual catalysis: (a) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012,** *3*, 633; (b) Inamdar, S. M.; Shinde, V. S.; Patil, N. T. *Org. Biomol. Chem.* **2015,** *13*, 8116; (c) Fu, J.; Huo, X.; Li, B.; Zhang, W. *Org. Biomol. Chem.* **2017,** *15*, 9747; (d) Pye, D. R.; Mankad, N. P. *Chem. Sci.* **2017,** *8*, 1705.

(10) **3la** is not configurationally stable, as it slowly epimerized on silica gel. For characterization purposes, the ester group of **3la** was reduced by DIBAL-H after the allylation. See SI for details.