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Amphiphilic π-Allyliridium *C,O*-Benzoates Enable Regio- and Enantioselective Amination of Branched Allylic Acetates Bearing Linear Alkyl Groups

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Supporting Information

ABSTRACT: The first examples of amphiphilic reactivity in the context of enantioselective catalysis are described. Commercially available π-allyliridium *C,O*-benzoates, which are stable to air, water and SiO_2 chromatography, and are well-known to catalyze allyl acetate-mediated carbonyl allylation, are now shown to catalyze highly chemo-, regio- and enantioselective substitutions of branched allylic acetates bearing linear alkyl groups with primary amines.

Since the discovery of the Tsuji−Trost reaction,[1] diverse catalytic systems for metal catalyzed allylic substitution have emerged.[2] Among the many useful transformations based on this pattern of reactivity, enantioselective iridium catalyzed aminations figure prominently.[3−11] Largely due to the pioneering work of Takeuchi,[3,4] Helmchen,[5,6] Hartwig,[7,8] Carreira[9] and You,[10,11] a broad range of amine nucleophiles can now be accommodated in highly regio- and enantioselective reactions of linear or branched allylic acetates (and in certain cases allylic alcohols).[3−11] Two classes of iridium catalysts may be distinguished on the basis of their ability to promote regio- and enantioselective reactions of either linear or branched allylic acetates (Figure 1). For type I catalysts, linear allyl proelectrophiles are used under basic conditions. For type II catalysts, branched allyl proelectrophiles are used under acidic conditions. Whereas type I catalysts are modified by one phosphoramidite and one external diene ligand, type II catalysts incorporate an internal *mono*-olefin ligand and two π-acidic phosphoramidites, which may account for their exceptional electrophilicity. The internal olefin of type II catalysts may enhance enantioselectivity in reactions of branched allyl proelectrophiles by displacing the π-bond of (σ+π)-allyl (enyl) iridium intermediates,[12] thus enabling rapid π-facial interconversion in otherwise stereospecific substitutions.[13]

Both type I and II catalysts bear π-acidic ligands and a formal positive charge at the metal center. These features enforce electrophilic properties of the allyliridium intermediate. In contrast, we have developed π-allyliridium *C,O*-benzoates, which are neutral and incorporate relatively strong σ-donor ligands (Figure 1).[14,15] As demonstrated by their ability to promote diverse allylative carbonyl additions, the supporting ligands of this catalyst confer nucleophilic character onto the allyl moiety.[16] However, as observed in our initial studies,[14b] carbonyl

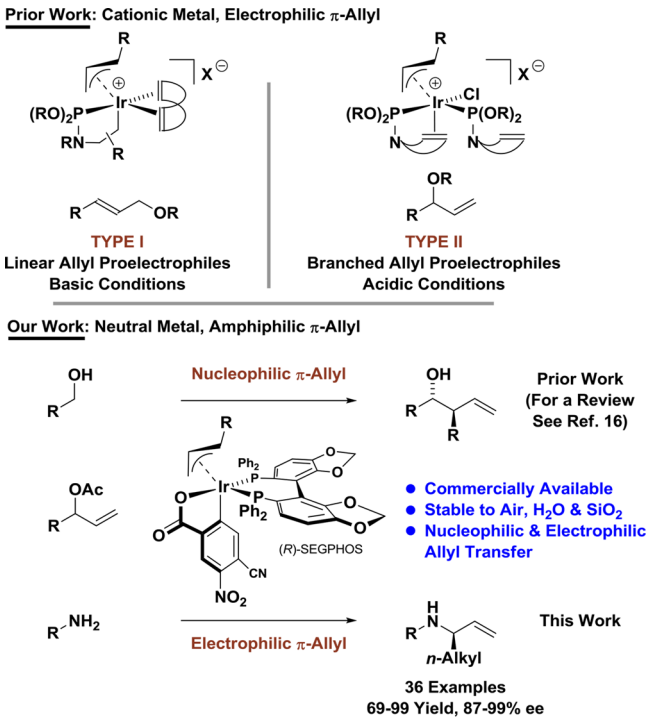

Figure 1. Phosphoramidite modified iridium complexes and amphiphilic π-allyliridium *C,O*-benzoates for regio- and enantioselective allylic amination.

allylation is often accompanied by small quantities of *O*-allylation, suggesting amphiphilic character of these π-allyl complexes. Pursuant to an accumulation of similar observations by coauthors at Genentech, a systematic attempt to evoke electrophilic behavior was undertaken in the context of allylic amination. Here, we show that the commercially available π-allyliridium *C,O*-benzoate modified by SEGPHOS catalyzes asymmetric allylic amination. This catalyst overcomes a significant limitation in scope across all known catalytic systems, the ability to engage branched allylic acetates bearing linear alkyl groups with uniformly high levels of regio- and enantioselectivity.[3−11,17−18]

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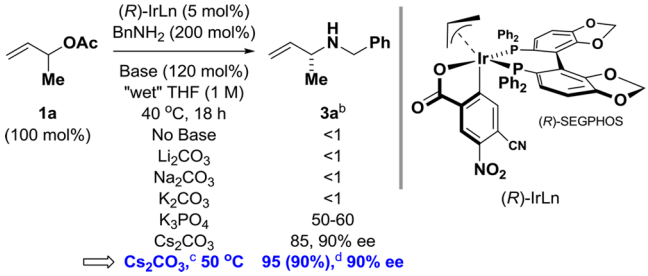
Table 1. Influence of Base in the Amination of α-Methyl Allyl Acetate 1a To Form Allylic Amine 3a[a]

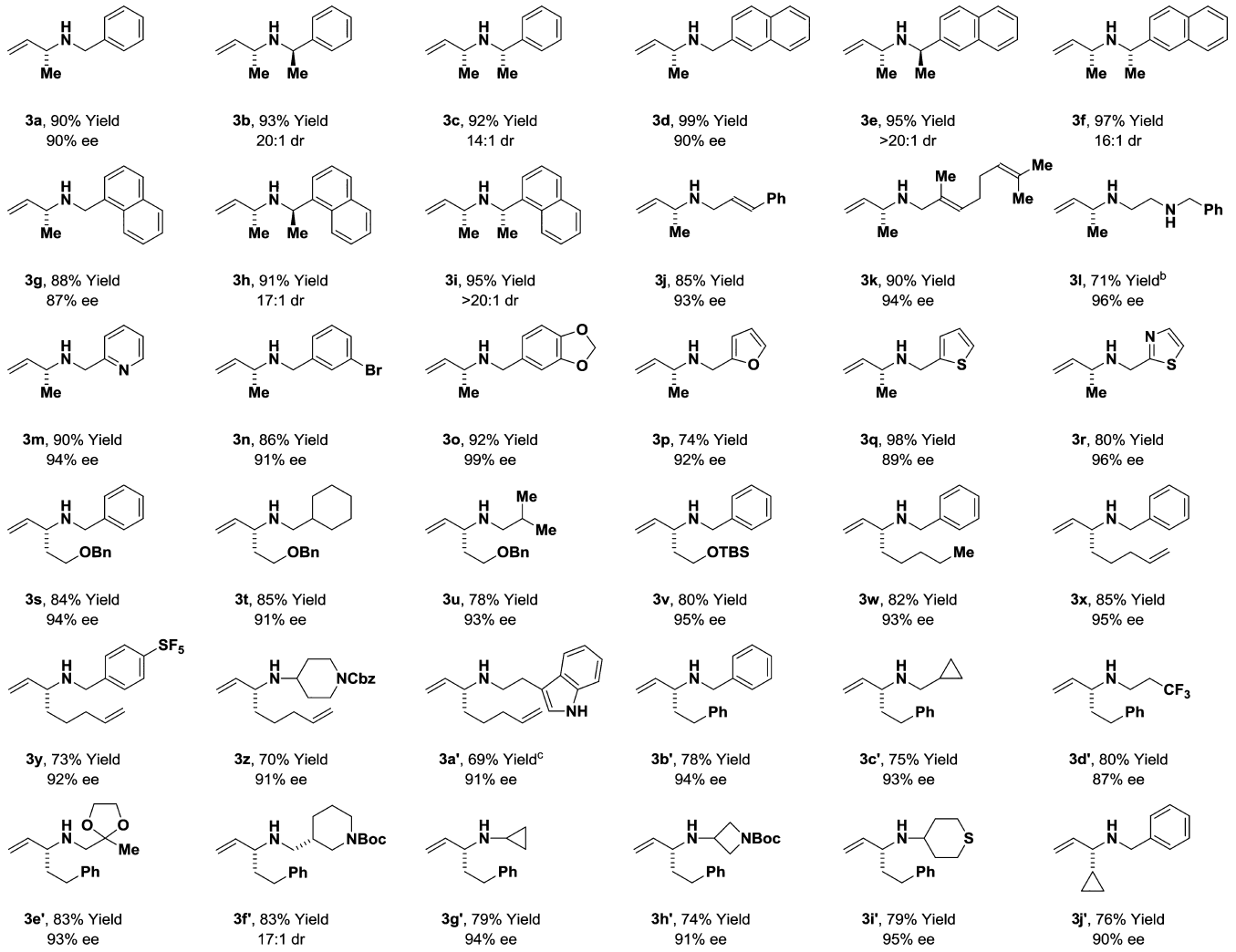


[a]All reactions were performed on a 0.44 mmol scale. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details. [b]Conversion was determined by ^{1}H NMR. [c]Cs_2CO_3 (200 mol%). [d]Yield of material isolated by silica gel chromatography.

In an initial set of experiments, α-methyl allyl acetate **1a** (100 mol%) was exposed to benzyl amine **2a** (200 mol%) in the presence of the SEGPHOS modified π-allyliridium *C*,*O*-benzoate (5 mol%) in THF (1 M) at 40 °C (Table 1). In the absence of base, products of amination were not observed. However, after screening various heterogeneous bases, it was found that reactions conducted in the presence of Cs_2CO_3 (120 mol%) provided the desired product of allylic amination **3a** exclusively as the branched regioisomer with high levels of enantiomeric enrichment. After further optimization, the allylic amine **3a** could be obtained in 90% isolated yield as a single regioisomer in 90% enantiomeric excess. Wet THF solvent is required, perhaps to partially solubilize Cs_2CO_3. Using distilled THF under otherwise optimal conditions, **3a** was obtained in only 61% yield. Optimal yields were restored using distilled THF in combination with water (250 mol%). The absolute stereochemistry of **3a** was determined by comparison of its optical rotation to that of an authentic sample reported in the literature (and X-ray analysis of **3j′**).[20]

Under these optimized conditions, primary benzylic, allylic and aliphatic amines serve as nucleophilic partners in aminations of diverse branched allylic acetates (Table 2). Complete branched-regioselectivity was accompanied by high levels of

Table 2. Regio- and Enantioselective Iridium-Catalyzed Amination of Branched Allylic Carboxylates[a]



[a]Yields of material isolated by silica gel chromatography. Standard conditions: (*R*)-IrLn (5 mol%), amine (200 mol%), Cs_2CO_3 (200 mol%), "wet" THF (1 M), 50 °C. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details. [b]$H_2NCH_2CH_2NHBn$ (400 mol%), ee% determined at the stage of **4l** (eq 1). [c]The cyclometalated iridium catalyst modified by the Roche ligand was used.[19]

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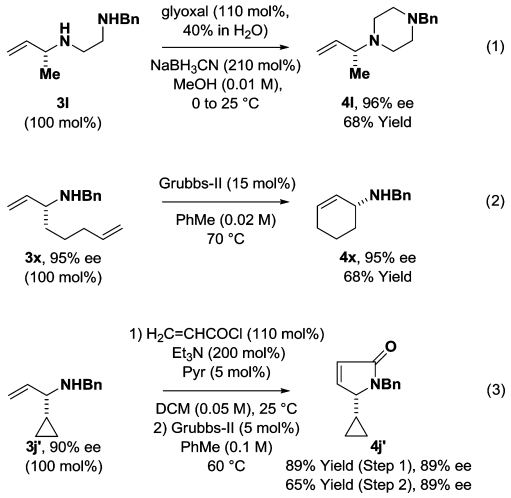


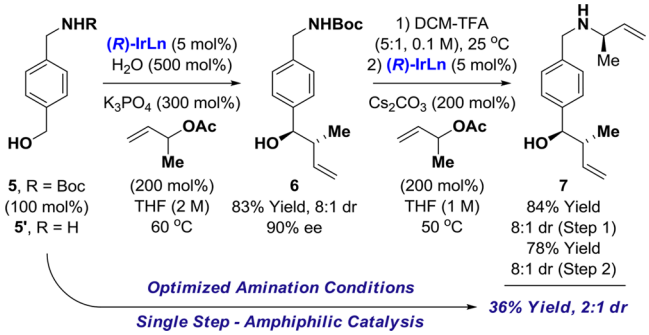
enantioselectively (^{1}H NMR and HPLC). Additionally, the levels of chemoselectivity in favor of primary amine allylation were sufficiently high that *N*-benzyl ethylene diamine and tryptamine could be converted to the respective amination products **3l** and **3a′** without competing allylation of the secondary amine. As demonstrated by the formation of **3z**, **3g′**, **3h′**, **3i′**, primary amines that are branched at the α-position are effective nucleophilic partners. Further, as illustrated by the formation of **3b** vs **3c**, **3e** vs **3f** and **3h** vs **3i**, excellent levels of catalyst-directed stereoinduction are observed. Perhaps the most notable feature of this catalytic system, however, resides in the ability to engage branched allylic acetates bearing linear alkyl groups in highly regio- and enantioselective aminations, a capability that complements the scope of previously reported iridium catalysts for allylic amination.[3−11,17,18]

To illustrate the utility of the reaction products a series of transformations were performed. The *N*-benzyl ethylene diamine adduct **3l** was subjected to reductive amination with glyoxal to form the piperazine **4l** (eq 1).[21] Adducts **3x** and **3j′** were converted to 1-(*N*-benzyl-amino)-2-cyclohexene **4x** (eq 2)[22] and the cyclopropyl substituted lactam **4j′** through ring-closing metathesis (eq 3).[5g]

Although numerous reports of "umpoled allylations" exist,[23] the amphiphilic properties displayed by π-allyliridium *C*,*O*-benzoates appear quite unique.[24] The same catalyst, (*R*)-IrLn (5 mol%), will promote both nucleophilic and electrophilic allylation under very similar conditions. For example, under standard amination conditions, 4-aminomethyl-benzyl alcohol and α-methyl allyl acetate are directly converted to compound **7** in 36% yield. Alternatively, compound **5** can be converted to compound **7** in a stepwise manner with higher levels of stereoselectivity using the same iridium catalyst (Scheme 1).

The nature of the C−N bond forming event merits discussion. For related enantioselective iridium catalyzed allylic aminations, an outer-sphere mechanism is postulated.[3−11] Though it is likely such pathways are also operative in aminations catalyzed by π-allyliridium *C*,*O*-benzoates, an inner-sphere mechanism cannot be excluded. The more stringent steric constraints of an inner-sphere mechanism may account for the fact that primary amines engage in allylation while secondary amines do not. Furthermore, enantiofacial selectivity for amination through an inner sphere mechanism matches that observed in nucleophilic allylations of α-substituted allylic acetates (Figure 2). Computational studies are underway to evaluate outer vs inner sphere pathways.

Scheme 1. Identical π-Allyliridium *C*,*O*-Benzoate Complexes Promote Both Nucleophilic and Electrophilic Allylation[a]



[a]See Supporting Information for further experimental details.

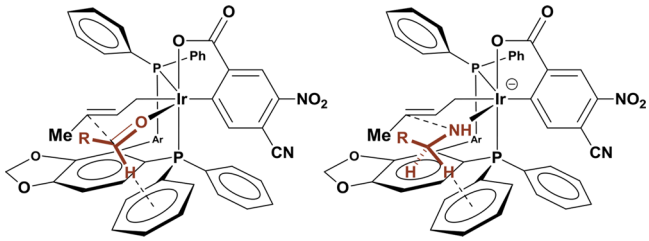


Figure 2. Stereochemical models accounting for equivalent π-facial selectivity in crotylation and amination.

In summary, highly tractable and commercially available π-allyliridium *C*,*O*-benzoates, which are well-known to catalyze nucleophilic carbonyl allylation, are now shown to catalyze chemo-, regio- and enantioselective electrophilic aminations of branched allylic acetates bearing linear alkyl groups. These processes broaden access to chiral *N*-containing building blocks[25] and establish unique amphiphilic properties of π-allyliridium *C*,*O*-benzoates, which should inform the design of new catalytic processes. More broadly, this work demonstrates how academic-industrial collaboration accelerates the discovery of robust, innovative methods for chemical synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b13482.

Experimental procedures and spectral data. HPLC traces of racemic and enantiomerically enriched products (PDF)
Crystallographic data for **3j′** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387. (b) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.

(2) For selected reviews on metal catalyzed allylic substitution, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580. (d) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (e) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (f) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (g) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147. (h) Moberg, C. *Top. Organomet. Chem.* **2011**, *38*, 209. (i) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467. (j) Oliver, S.; Evans, P. A. *Synthesis* **2013**, *45*, 3179. (k) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44*, 7929. (l) Trost, B. M. *Tetrahedron* **2015**, *71*, 5708.

(3) (a) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. (b) Onodera, G.; Watabe, K.; Matsubara, M.; Oda, K.; Kezuka, S.; Takeuchi, R. *Adv. Synth. Catal.* **2008**, *350*, 2725.

(4) Reviews: (a) Takeuchi, R. *Synlett* **2002**, 1954. (b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, *2006*, 3349.

(5) (a) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, *2002*, 2569. (b) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116. (c) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896. (d) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. (e) Weihofen, R.; Dahnz, A.; Tverskoy, O.; Helmchen, G. *Chem. Commun.* **2005**, 3541. (f) Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546. (g) Spiess, S.; Berthold, C.; Weihofen, R.; Helmchen, G. *Org. Biomol. Chem.* **2007**, *5*, 2357. (h) Spiess, S.; Raskatov, J. A.; Gnamm, C.; Brödner, K.; Helmchen, G. *Chem. - Eur. J.* **2009**, *15*, 11087. (i) Gärtner, M.; Jäkel, M.; Achatz, M.; SonnenSchein, C.; Tverskoy, O.; Helmchen, G. *Org. Lett.* **2011**, *13*, 2810.

(6) Reviews: (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (b) Helmchen, G. In *Iridium Complexes in Organic Synthesis*; Oro, L. A., Claver, C., Eds.; Wiley-VCH: Weinheim, 2009; pp 211−250. (c) Qu, J.; Helmchen, G. *Acc. Chem. Res.* **2017**, *50*, 2539.

(7) (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. (c) Leitner, A.; Shu, C.; Hartwig, J. F. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5830. (d) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (e) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506. (f) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093. (g) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770. (h) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508. (i) Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 11680. (j) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949.

(8) Reviews: (a) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (b) Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169.

(9) (a) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (b) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917. (c) Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3470. (d) Rossler, S. L.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2017**, *139*, 3603.

(10) (a) Ye, K.-Y.; Dai, L.-X.; You, S.-L. *Org. Biomol. Chem.* **2012**, *10*, 5932. (b) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 5183. (c) Ye, K.-Y.; Zhao, Z.-A.; Lai, Z.-W.; Dai, L.-X.; You, S.-L. *Synthesis* **2013**, *45*, 2109. (d) Ye, K.-Y.; Dai, L.-X.; You, S.-L. *Chem. - Eur. J.* **2014**, *20*, 3040. (e) Yang, Z.-P.; Wu, Q.-F.; You, S.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6986. (f) Zhang, X.; Yang, Z.-P.; Huang, L.; You, S.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1873. (g) Yang, Z.-P.; Wu, Q.-F.; Shao, W.; You, S.-L. *J. Am. Chem. Soc.* **2015**, *137*, 15899. (h) Ye, K.-Y.; Cheng, Q.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2016**, *55*, 8113. (i) Zhang, X.; Liu, W.-B.; Cheng, Q.; You, S.-L. *Organometallics* **2016**, *35*, 2467. (j) Yang, Z.-P.; Zheng, C.; Huang, L.; Qian, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2017**, *56*, 1530.

(11) (a) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2011**, *38*, 155. (b) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (c) Wu, W.-T.; Zhang, L.; You, S.-L. *Chem. Soc. Rev.* **2016**, *45*, 1570.

(12) For spectroscopic and crystallographic evidence of a stable rhodium enyl complex and its role in enabling regio- and stereospecific rhodium catalyzed allylic substitution, respectively, see: (a) Lawson, D. N.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1733. (b) Tanaka, I.; Jin-no, N.; Kushida, T.; Tsutsui, N.; Ashida, T.; Suzuki, H.; Sakurai, H.; Moro-oka, Y.; Ikawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 657. (c) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(13) Beyond the rather complex effects of Lewis basic additives (refs 5a 6a, vs 6b), highly π-acidic ligands are required to preserve stereospecificity in iridium catalyzed reactions of branched allyl proelectrophiles: Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741.

(14) For initial reports, see: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514.

(15) For preparation and chromatographic purification of the iridium catalyst in 85% yield, see: Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, *76*, 2350.

(16) For a recent overview of enantioselective allylations and propargylations catalyzed by π-allyliridium *C,O*-benzoates, see: Kim, S. W.; Zhang, W.; Krische, M. J. *Acc. Chem. Res.* **2017**, *50*, 2371.

(17) For other enantioselective metal catalyzed allylic aminations employing diverse allyl proelectrophiles, see: (a) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876. (b) Arnold, J. S.; Nguyen, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 8380. (c) Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392. (d) Xu, K.; Wang, Y.-H.; Khakyzadeh, V.; Breit, B. *Chem. Sci.* **2016**, *7*, 3313. (e) Mwenda, E. T.; Nguyen, H. M. *Org. Lett.* **2017**, *19*, 4814. (f) Guo, W.; Cai, A.; Xie, J.; Kleij, A. W. *Angew. Chem., Int. Ed.* **2017**, *56*, 11797.

(18) For selected reviews on the catalytic enantioselective synthesis of allylic amines, see: (a) Cannon, J. S.; Overman, L. E. *Acc. Chem. Res.* **2016**, *49*, 2220. (b) Grange, R. L.; Clizbe, E. A.; Evans, P. A. *Synthesis* **2016**, *48*, 2911. (c) Fernandes, R. A.; Kattanguru, P.; Gholap, S. P.; Chaudhari, D. A. *Org. Biomol. Chem.* **2017**, *15*, 2672.

(19) An enantiomeric enrichment of 82% ee was observed using the SEGPHOS-modified catalyst. For the Roche ligand, see: (a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897. (b) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370.

(20) (a) Vrieze, D. C.; Hoge, G. S.; Hoerter, P. Z.; Van Haitsma, J. T.; Samas, B. M. *Org. Lett.* **2009**, *11*, 3140. (b) Höcker, J.; Rudolf, G.; Bächle, F.; Fleischer, S.; Lindner, B. D.; Helmchen, G. *Eur. J. Org. Chem.* **2013**, *2013*, 5149.

(21) Lee, B. K.; Kim, M. S.; Hahm, H. S.; Kim, D. S.; Lee, W. K.; Ha, H.-J. *Tetrahedron* **2006**, *62*, 8393.

(22) For a related RCM, see: Edwards, A. S.; Wybrow, R. A. J.; Johnstone, C.; Adams, H.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1542.

(23) For selected reviews on carbonyl allylation via umpolung of π-allyls, see: (a) Masuyama, Y. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1994; Vol. 3, p 255. (b) Tamaru, Y. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley: New York, 2002; Vol. 2, pp 1917. (c) Tamaru, Y. In *Perspectives in Organopalladium Chemistry for the XXI Century*; Tsuji, J., Ed.; Elsevier: Amsterdam, 1999; pp 215. (d) Kondo, T.; Mitsudo, T.-A. *Curr. Org. Chem.* **2002**, *6*, 1163. (e) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, *2005*, 2647. (f) Zanoni, G.;

DOI: 10.1021/jacs.7b13482
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, *2007*, 3599.

(24) Amphiphilic properties were postulated in palladium catalyzed conjugate allylation-allylic alkylations of alkylidene malononitriles and related compounds. The requirement of both allyltributylstannane and allylic chloride suggests these reactions do not involve amphiphilic π-allylpalladium intermediates: (a) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113. For related processes, see: (b) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (c) Nakamura, H.; Shimizu, K. *Tetrahedron Lett.* **2011**, *52*, 426. (d) Genady, A. R.; Nakamura, H. *Org. Biomol. Chem.* **2011**, *9*, 7180. (e) Nambo, M.; Wakamiya, A.; Itami, K. *Chem. Sci.* **2012**, *3*, 3474.

(25) For statistical analysis of the appearance of *N*-heterocycles in FDA approved drugs, see: Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

DOI: 10.1021/jacs.7b13482
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX