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Enantioselective Iridium-Catalyzed Allylic Cyclizations

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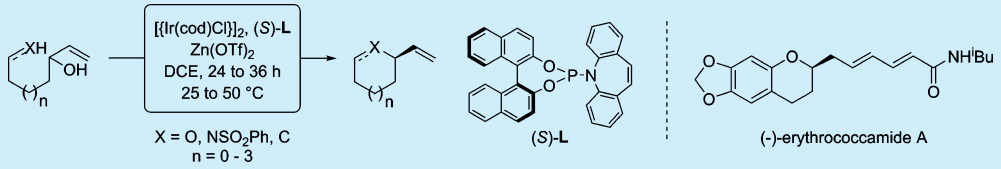
Supporting Information

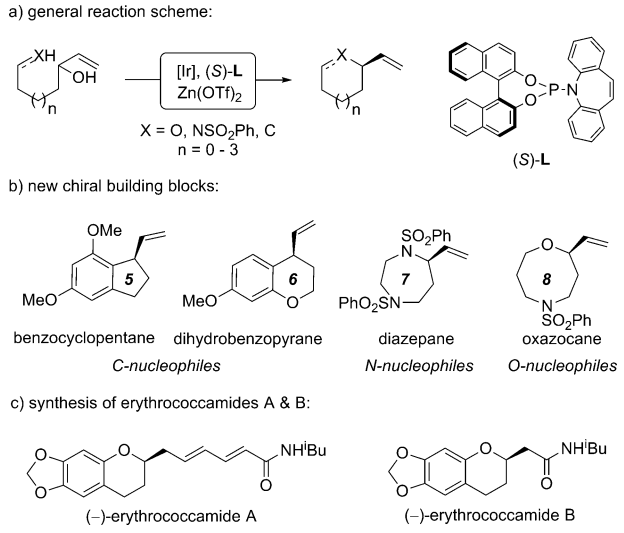


ABSTRACT: A method for the enantioselective synthesis of carbo- and heterocyclic ring systems enabled through the combination of Lewis acid activation and iridium-catalyzed allylic substitution is described. The reaction proceeds with branched, allylic alcohols and carbon nucleophiles as well as heteronucleophiles to give a diverse set of ring systems in good yields and with high enantioselectivities. The utility of the method is highlighted by the asymmetric syntheses of erythrococcamides A and B.

Hetero- and carbocycles are ubiquitous in natural isolates and in synthetic drugs with diverse modes of action.[1] The development and improvement of cross-coupling chemistry has widened the availability of aromatic building blocks, which ultimately led to an increased aromatic ring count in small molecule drugs.[2,3] However, recent data indicate that there is a limit to the aromatic ring count beyond which it becomes detrimental for the development of drug candidates.[4] As a way around such limitations, saturated rings can impart beneficial effects in terms of pharmacokinetics, solubility, or bioavailability.[5] Hence, the discovery of simple catalytic methods that rapidly provide sets of structurally diverse saturated (hetero)cyclic motifs is desirable. Herein, we report a general and direct Ir-catalyzed, enantioselective, allylic cyclization of unactivated, branched allylic alcohols with oxygen- and nitrogen-based heteronucleophiles, as well as electron-rich aromatic substrates (Scheme 1a and b).[6] The practicality of the approach is demonstrated with the enantioselective syntheses of erythrococcamides A and B (Scheme 1c).

Significant research efforts have focused on the development of enantioselective, catalytic methods for the preparation of *N*-heterocycles (e.g., pyrrolidines, piperidines, piperazines, tetrahydroquinolines), *O*-heterocycles (e.g., oxanes, dioxanes), and carbocycles (tetrahydrocarbazole, tetrahydrobenzpyrane).[7] Among them, the application of iridium-catalyzed, enantioselective, allylic cyclization has recently attracted attention. Helmchen has reported intramolecular Ir-catalyzed allylic aminations using phosphoramidite ligands in combination with bases to promote the formation of 5- to 7-membered rings.[8] An intramolecular allylic amidation reaction for the synthesis of tetrahydroisoquinolines as well as 5- and 6-membered rings was developed by Feringa and co-workers.[9] Additionally, the You group recently disclosed several approaches for intramolecular allylic substitution reactions with amines and carbon nucleophiles (indoles, pyrroles, and phenols).[10]

Scheme 1. Enantioselective Iridium-Catalyzed Allylic Cyclizations



It is important to note, however, that common to these protocols are different requirements in the reaction conditions (solvents, promoters, ligands, or metal precursors) for incorporation of various (hetero)nucleophiles and preparation of different ring sizes. Furthermore, the use of a stoichiometric amount of base and activation of the allylic alcohol as a carbonate or acetate are often required. The incorporation of activating groups leads to longer, less straightforward substrate syntheses and to sequences that are suboptimal vis a vis atom economy.

We have previously reported the direct substitution of branched allylic alcohols with a variety of nucleophiles.[11] In

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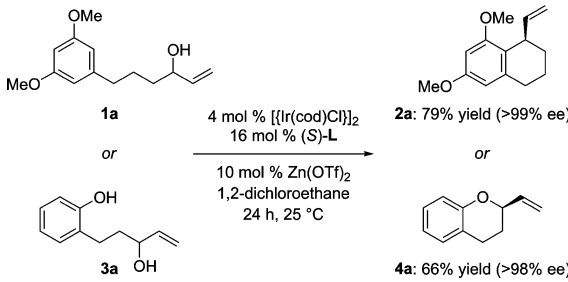
light of our report on Ir-catalyzed, zinc triflate promoted polyene cyclizations we were interested in expanding this approach to access a broader range of chiral, cyclic building blocks.[12] To evaluate the potential of the [Ir]/$Zn(OTf)_2$ system to promote allylic cyclizations with various nucleophiles, we subjected allylic alcohol substrate **1a** to the reaction conditions shown in Scheme 2, and we were pleased to observe

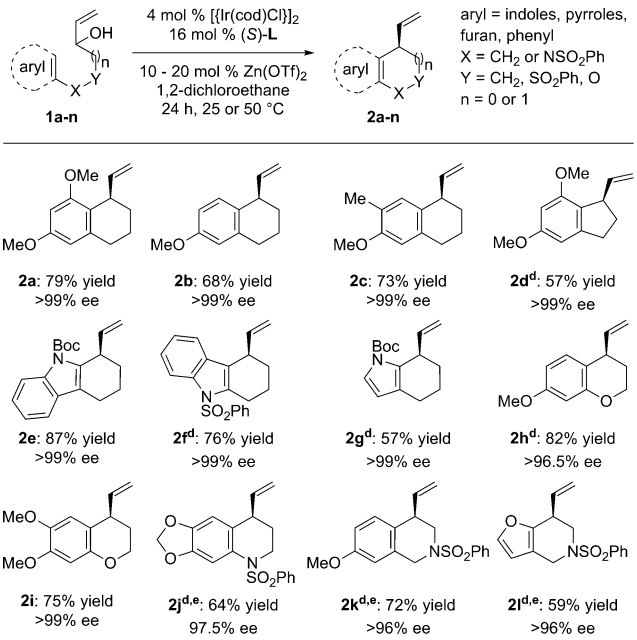
Scheme 2. Initial Results



the formation of cyclization product **2a** in 79% yield with excellent enantioselectivity (>99% ee, Scheme 2). Phenol substrate **3a** bearing a nucleophilic alcohol readily cyclized under identical conditions to give the corresponding dihydrobenzopyran derivative **4a** in 66% yield and >98% ee (Scheme 2).[13]

With these promising results in hand, the generality and scope of the reaction was examined. The initial focus was on the use of sp^2-carbon nucleophiles to generate fused ring systems (Scheme 3). The reaction proceeded well with electron-rich alkoxy-substituted substrates to give products **2a–2c** in good yields and >99% ee (Scheme 3, entries **2a–2c**). Interestingly, the use of arenes **2b–2c** led to exclusive

Scheme 3. Reaction Scope with Carbon Nucleophiles[a,b,c]



[a]Unless noted otherwise all reactions were conducted on 0.25 mmol scale under standard conditions (4 mol % [Ir], 16 mol % (*S*)-**L**, 10 mol % $Zn(OTf)_2$ at 25 °C for 24 h). [b]Yields of isolated products. [c]% ee determined by SFC on a chiral stationary phase. [d]Conducted with 20 mol % $Zn(OTf)_2$. [e]Conducted at 50 °C.

cyclization at the position *para* to the methoxy substituent. This stands in contrast to our previous observations in a polyene cyclization reaction where both regioisomers were isolated (2:1 *para*/*ortho* selectivity). It also highlights a difference to the method by You and co-workers where product mixtures in favor of *ortho* functionalization were usually observed (1:4 to 1:6 *para*/*ortho* selectivity).[10d] The formation of five-membered rings employing this method was successful, furnishing the fused rings with >99% ee (**2d**). Substrates incorporating hetarenes smoothly underwent cyclization, as showcased with the examples of indoles (**2e–2f**) and pyrrole (**2g**). Next, we turned our attention to substrates that incorporate heteroatom tethers, leading to saturated heterocyclic products. Substrates derived from phenols (**2h–2i**) and anilines (**2j**) provided the corresponding dihydrobenzopyran and tetrahydroquinoline products, respectively. In a similar manner, tetrahydroisoquinoline (**2k**) and furanopiperidine **2l** were obtained in good yields with excellent enantioselectivities. For substrates **2h–2k** no cyclization at the *ortho* position was observed, and, consequently, the products were isolated as single isomers.[14] We suggest steric interactions between the substituent on the aromatic ring of the substrate and the ligand on the active iridium species as a possible explanation for this exclusive *para* selectivity (Figure 1). This hypothesis is

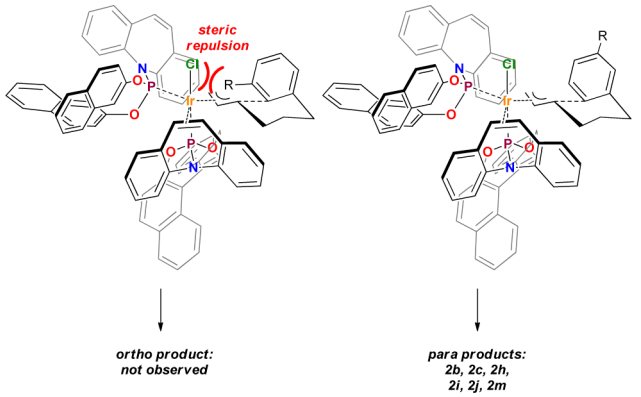


Figure 1. Transition state models leading to the *ortho* or *para* substituted products, respectively.

supported by a model based on our recent mechanistic studies involving X-ray characterization of a catalytically active Ir(III) species, which highlights steric repulsion between the azepine moiety of the non-chelating ligand with the *ortho* substituent.[15] Such repulsive interactions would be minimized for the intermediate/transition state leading to the *para* substituted product.

Next, we sought to examine the scope of oxygen and nitrogen nucleophiles. The optimal conditions for the production of **4a** allowed a lower Ir-catalyst loading (2 mol % $[Ir(cod)Cl]_2$, 8 mol % (*S*)-**L**, 20 mol % $Zn(OTf)_2$) while affording higher yields of the cyclization product (79% yield, 98% ee, Scheme 4, entry **4a**). In a similar manner, 5-membered dihydrobenzofuran derivative **4b** was obtained in 88% yield and 96.5% ee. The use of aliphatic alcohols as substrates for cyclization was evaluated next. Under standard conditions, 6-membered tetrahydropyran and dioxane derivatives were obtained in good yield and with good enantioselectivities (**4c–4d**). 1,6- and 1,7-Diol substrates readily cyclized to give the corresponding 7- and 8-membered, medium-sized rings. The set of products includes derivatives of oxepane (entry **4e**),

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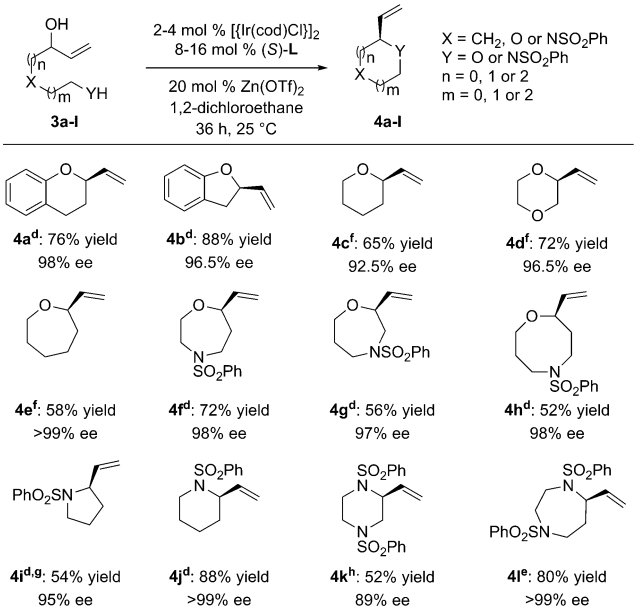
Scheme 4. Reaction Scope with Heteroatom Nucleophiles[a,b,c]

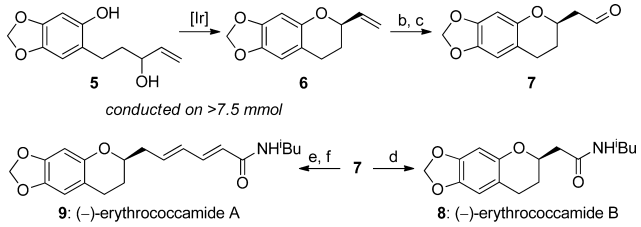


[a]Unless noted otherwise all reactions were conducted on 0.25 mmol scale under standard conditions (4 mol % [Ir], 16 mol % (*S*)-**L**, 20 mol % $Zn(OTf)_2$ at 25 °C for 36 h). [b]Yields of isolated products. [c]% ee determined by SFC on a chiral stationary phase. [d]Conducted with 2 mol % $[\{Ir(cod)Cl\}]_2$, 8 mol % (*S*)-**L**. [e]Conducted at 50 °C. [f]Due to high volatility isolated as the corresponding benzoate, after hydroboration; see Supporting Information for further information. [g]At 50 °C isolated in 84% yield with 90% ee. [h]At 50 °C isolated in 92% yield with 65% ee.

oxazepane (entries **4f**–**4g**), and oxazocane (entry **4h**). It is important to note that formation of product resulting from the alternative intermolecular pathway was only observed in one instance (entry **4h**). Conducting the reaction at higher dilution did not improve the yield of the desired product. Nitrogen based nucleophiles in the intramolecular allylic substitution reaction were subsequently examined. The corresponding 1,4-, 1,5-, and 1,6-sulfonamide–alcohol substrates readily cyclized to give enantioenriched pyrrolidine (entry **4i**), piperidine (entry **4j**), piperazine (entry **4k**), and diazepane derivatives (entry **4l**). However, the yields for **4i** and **4k** were improved when the reaction was performed at elevated temperature (50 °C), albeit with reduction of enantioselectivities.

To highlight the synthetic utility of the $[Ir]/Zn(OTf)_2$ cyclization method beyond the generation of simple building blocks, enantioselective syntheses of erythrococcamides A and B were conducted (Scheme 5). These isobutylamides were isolated from *Dinosperma erythrococca*, and to date, only a single enantioselective synthesis of erythrococcamide B has been reported.[16,17] Starting from sesamol, the cyclization substrate **5** was prepared in 3 steps, which when subjected to $[Ir]/Zn(OTf)_2$ afforded cyclization product **6** in 80% yield and >98% ee (reaction was performed on >7.5 mmol scale). The side chain was installed by hydroboration, followed by oxidative workup and subsequent TEMPO oxidation of the alcohol to the corresponding aldehyde **7** (79% yield over 2 steps). Pinnick oxidation of aldehyde **7** and direct amide bond formation of the crude carboxylic acid with isobutylamine afforded *ent*-erythrococcamide B (**8**) in 87% yield over 2 steps. In the synthesis of erythrococcamide A, Wittig reaction of aldehyde **7** with a stabilized ylidene resulted in an intermediate ester (1:1 mixture of diastereomers), which, following treatment with iodine, furnished a 9:1 (*E*)/(*Z*)-mixture. Saponification of the ester followed by amide bond formation with isobutylamine afforded *ent*-erythrococcamide A (**9**) in 92% yield over 2 steps.

Scheme 5. Total Syntheses of Erythrococcamides A and B



[a]Standard conditions for $[Ir]/Zn(OTf)_2$, 80%, 98.5% ee. [b]2.0 equiv of 9-BBN, THF, 60 °C, 16 h; then 10.0 equiv of $NaBO_3{\cdot}4H_2O$, 0 to 25 °C, 24 h, 93%. [c]20 mol % TEMPO, 1.2 equiv of $PhI(OAc)_2$, CH_2Cl_2, 25 °C, 2 h, 85%. [d]Pinnick oxidation: 12.0 equiv of 2-methyl-2-butene, 5.0 equiv of $NaClO_2$, H_2O, 0 to 25 °C, 3 h; then subsequent amide coupling, 4.0 equiv of 2-methylpropan-1-amine, 2.0 equiv of HATU, DMF, 0 to 25 °C, 16 h, 87% over 2 steps. [e]2.0 equiv of (*E*)-methyl 4-(triphenylphosphoranylidene)but-2-enoate, CH_2Cl_2, 25 °C, 2.5 h, then 1 mol % I_2, benzene, reflux, 5 h, 65%, *E*/*Z* = 9:1. [f]3.0 equiv of LiOH, THF/MeOH, 25 °C, 16 h, then 4.0 equiv of 2-methylpropan-1-amine, 2.0 equiv of HATU, DMF, 0 to 25 °C, 16 h, 92% yield over 2 steps.

In conclusion, we have developed a uniform method for the enantioselective, intramolecular allylic substitution reaction with aliphatic alcohols, sulphonamides, and electron-rich arenes as nucleophiles. The method enables the preparation of a unique set of heterocyclic ring systems via user-friendly and scalable conditions. The utility and generality of the method was showcased through the syntheses of erythrococcamides A and B.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01346.

Detailed experimental procedures, and characterization data and copies of ^1H, ^{13}C NMR spectra and SFC traces of the products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For examples, see: (a) Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*; Thieme: New York, 2001. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1.

(2) A recent review and references therein: Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809.

(3) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijerer, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

(4) Ritchie, T. J.; Macdonald, S. J. F. *Drug Discovery Today* **2009**, *14*, 1011.

(5) Leeson, R. D.; St-Gallay, S. A.; Wenlock, M. C. *MedChemComm* **2011**, *2*, 91.

(6) To the best of our knowledge, this is the first report of a general, enantioselective, intramolecular Ir-catalyzed allylic etherification reaction. To date only two isolated examples have been reported: (a) See ref 8b. (b) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185.

(7) For selected examples, see: (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (d) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. (e) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327. (f) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801. (g) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784. (h) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808. (i) Tanaka, S.; Seki, T.; Kitamura, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8948.

(8) (a) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. N. *Chem. Commun.* **2004**, 896−897. (b) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239. (c) Spiess, S.; Welter, C.; Franck, G.; Taquet, J.-P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7652.

(9) Teichert, J. F.; Fañanás-Mastral, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 688.

(10) (a) Zhuo, C.-X.; Wu, Q.-F.; Zhao, Q.; Xu, Q.-L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 8169. (b) Xu, Q.-L.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2013**, *15*, 5909. (c) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chem. Sci.* **2013**, *4*, 97. (d) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2012**, *14*, 2579. (e) Ye, K.-Y.; Cheng, Q.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2016**, *55*, 8113. (f) Yang, Z.-P.; Wu, Q.-F.; Shao, W.; You, S.-L. *J. Am. Chem. Soc.* **2015**, *137*, 15899. (g) Zhuo, C.-X.; Cheng, Q.; Liu, W.-B.; Zhao, Q.; You, S.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8475.

(11) Amine and oxygen nucleophiles: (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. Vinyl- and alkyne tetrafluoroborates: (d) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994. (e) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532. Olefins: (f) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3006. Dual catalysis with chiral amines and aldehydes: (g) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065. (h) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3020. (i) Sandmeier, T.; Krautwald, S.; Zipfel, H. F.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 14363. Organozinc compounds: (j) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 7644. Hydrazones: (k) Breitler, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2015**, *137*, 5296. Allylsilanes: (l) Hamilton, J. Y.; Hauser, N.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10759.

(12) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276.

(13) For more details on screening of different promoters and conditions, see Supporting Information.

(14) Importantly, for all cases examined, the potentially competitive intermolecular arylation pathway is completely suppressed. The only detectable byproduct is a linear ethyl ketone, resulting from isomerization of the corresponding allylic alcohol that was observed in some cases.

(15) Rössler, S. L.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2017**, *139*, 3603−3606.

(16) Latif, Z.; Hartley, T.; Rice, M.; Waigh, R.; Waterman, P. *J. Nat. Prod.* **1998**, *61*, 614−619.

(17) Azuma, T.; Murata, A.; Kobayashi, Y.; Inokuma, T.; Takemoto, Y. *Org. Lett.* **2014**, *16*, 4256−4259.

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