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Synthesis of the Taxol Core via Catalytic Asymmetric 1,4-Addition of an Alkylzirconium Nucleophile

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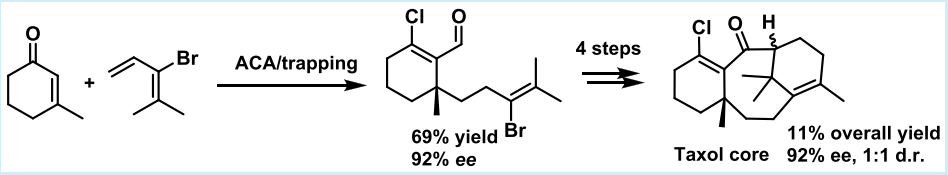


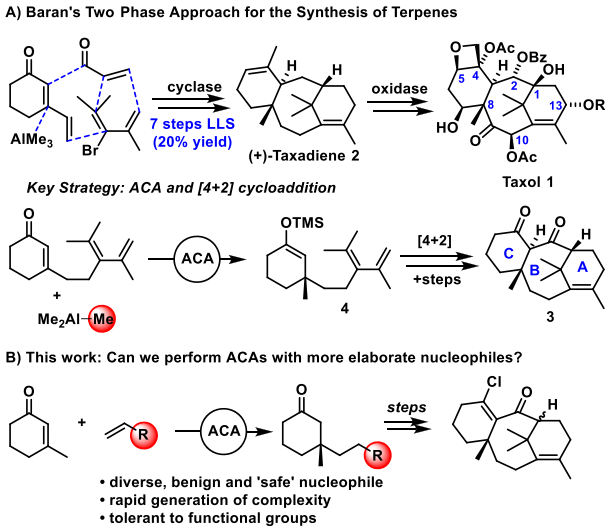
ABSTRACT: The Taxol core was prepared in five steps via a key copper-catalyzed asymmetric conjugate addition trapping sequence. The use of a bromodiene-derived alkylzirconium nucleophile followed by trapping with $POCl_3$/DMF gave a highly functionalized intermediate featuring a quaternary center in 69% yield with 92% ee. After 1,2-addition, Suzuki−Miyaura cross-coupling, allylic oxidation, and a type II intramolecular Diels−Alder reaction, the taxol core was obtained in 11% overall yield with 92% ee.

Taxol **1** (trademarked as paclitaxel) is a multibillion dollar anticancer drug. In the past, interest in this molecule stemmed from solving an issue of supply; Taxol was only available in appreciable quantities from the Yew tree, and harvesting from such a source was not sustainable.[1a] A significant effort was devoted toward the chemical synthesis of **1**, and many advances in organic chemistry were made by groups attempting to solve this challenging problem.[1b−j]

A recent strategy for the synthesis of terpenes proposed by Baran and coworkers involves first constructing the carbon-based framework of the molecule, followed by the installation of functional groups via a series of late-stage oxidations to give the target.[2a−c] Using this approach, oxidized taxanes, including Taxol itself, were prepared by the combination of a "cyclase" phase to form the carbon skeleton, followed by an "oxidase" phase to adjust the final oxidation state of the molecule (Scheme 1A).[2d,e] Thus the cyclase phase was implemented to provide Taxadiene **2** in seven steps in 20% overall yield. The brevity in the synthesis of **2** arises from two key features (Scheme 1B): the use of a type II intramolecular Diels−Alder reaction to prepare the A/B rings of **3**, a strategy shared by Shea and others to prepare taxane derivatives,[3] and a catalytic asymmetric conjugate addition (ACA) for the formation of **4** using Alexakis's protocol for Me addition.[4]

The latter of these tactics was the main inspiration for this project, and we wondered if we could add fragments more complex than simple alkyl units such as methyl (Scheme 1C). The nucleophiles traditionally used in ACAs (organozinc, organoaluminum, and Grignard reagents)[5] are limited to only very simple coupling partners. Furthermore, the use of these organometallic reagents imposes limits on which functional groups can be used and the applicability of these procedures in complex molecule synthesis. In 2013, we reported the formation of quaternary stereogenic centers[6] by ACA of alkylzirconium reagents[7] to enones.[8] The transformations are

Scheme 1. (A) Synthesis of (+)-Taxadiene by Baran and Coworkers and (B) This Work



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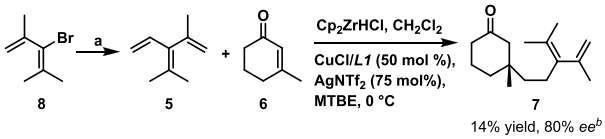
catalyzed by copper−phosphoramidite complexes, and the alkyl zirconocenes are generated in situ from alkenes and Cp_2ZrHCl via hydrometalation. Alkylzirconium reagents, when used in this fashion, can mitigate the aforementioned shortcomings of traditional nucleophiles because they are more tolerant toward functional groups. We hoped to use an appropriate fragment in the synthesis of the taxol core, but the precise choice of the precursor alkene was not immediately obvious. Also, it is more common than not that ACAs are sensitive to the solvent, temperature, concentration, method of addition, and presence of additives.[5]

In an approach that would have closely follow Baran's route to the core, conjugated triene **5**[9] was added to **6** (Scheme 2).

Scheme 2. Preparation of Intermediate 7 Using ACA of Triene 5[a]



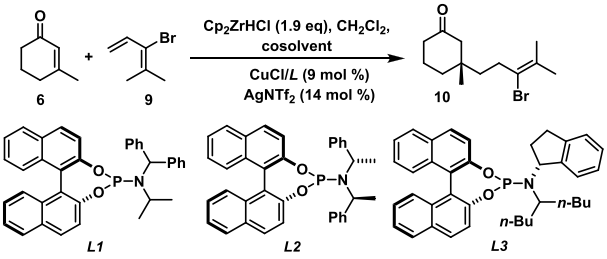
[a](a) Vinylmagnesium bromide (1.3 equiv), $ZnBr_2$ (2.0 equiv), $PdCl_2$·dppf (0.020 equiv), THF, 0 °C to rt, 6.5 h, 49%. (b) ee determined by SFC or HPLC. Abbreviations: dppf = 1,1′-bis(diphenylphosphino)-ferrocene.

Despite extensive optimization, **7** could be obtained in only 14% yield with 80% ee. Although disappointing, no side products that would result from hydrozirconation at the di- or tetrasubstituted olefins were observed, and we postulated that the low yield was due to the size of the polyene.

In our search for an alkene with a smaller steric profile, we encountered bromodiene **9**[10] first reported by Takahashi and coworkers. **9** was prepared from 3-methylcrotonaldehyde via bromination to the corresponding bromoaldehyde followed by Peterson olefination and could easily be made on a decagram scale. (See the Supporting Information for more details.)

The ACA of **9** to **6** was examined, and it was found that the phosphoramidite ligand has a tremendous effect on the enantioselectivity of this reaction (Table 1). **L1** and **L2** have both been used extensively in similar transformations[6a,7] but gave poor enantioselectivities for our system. To our delight, **L3**,[6a] developed in our group and used in other challenging transformations,[8e,11−13] was found to give the best yield/ee combination and is easily prepared. The investigation of different counterions (BF_4, SbF_6, OTf, PF_6, ClO_4) indicated that NTf_2 gave superior yields and enantioselectivity. Previous experiments in the group showed that using dichloromethane as a solvent was often beneficial. The use of a chlorinated cosolvent gave better enantioselectivity but lower yields. With hydrocarbon or ethereal cosolvents, higher yields but lower ee values were observed.

Table 1. Optimization of Key ACA Conjugate Addition Step[a]



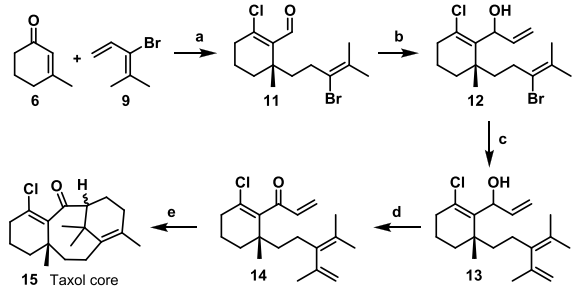
entry	L	cosolvent	yield (%)[b]	ee (%)[c]
1	1	MTBE	70	6
2	2	MTBE	63	18
3	3	MTBE	81	82
4	**3**	**DCE**	**45**	**90**
5	3	PhMe	71	88

[a]Reactions were performed on a 0.5 mmol scale using 2.4 equiv of **9**. [b]Isolated yields. [c]ee values were determined by SFC or HPLC analysis using a chiral nonracemic stationary phase.

Upon scale-up (to 3 mmol of **6**), the reaction performed better, and the product could be obtained in 96% yield with 88% ee. ACAs of alkylzirconium nucleophiles often work better when scaled up; this effect is attributed to the fact that it is easier to measure and mix the reaction components on larger scales, and larger scales minimize the impact of trace air and moisture.

Having demonstrated that **9** could reliably be added to **6**, we next turned our attention to the preparation of a suitable intermediate for the synthesis of the desired product. The trapping of zirconium enolates is a challenging problem,[14] and we recently reported trapping reactions using the Vilsmeier−Haack reagent to give β-chloroaldehydes from our ACA zirconium enolates.[15] It was found that this trapping protocol also worked for our substrate; using 16.5 mmol of **6**, 3.6 g of **11** (corresponding to 69% yield) could be obtained with 92% ee, requiring minimal modification (Scheme 3, steps a and b). (See the Supporting Information for optimization.)

Scheme 3. Completion of the Synthesis[a]



[a](a) Cp_2ZrHCl (1.9 equiv), CuCl/*L*3 (0.08 equiv), DCE/CH_2Cl_2, rt, 17 h; then, $POCl_3$/DMF (10 equiv), DCE, 60 °C, 1 h, 69%, 92% ee. (b) Vinylmagnesium bromide (1.2 equiv), Et_2O, 0 °C, 1 h, 87%. (c) Isopropenylboronic acid pinacol ester (1.1 equiv), $PdCl_2(PPh_3)_2$/dppf (0.10 equiv), K_3PO_4 (3.0 equiv), DMF, 65 °C, 17 h, 59%. (d) Dess−Martin periodinane (1.2 equiv), H_2O (0.50 equiv), CH_2Cl_2, rt, 30 min, undesired/desired 1:10, 90%. (e) $TiCl_4$ (1.1 equiv), slow addition, CH_2Cl_2, −35 °C, 6 h, 35%, 1:1 d.r., 92% ee. Abbreviations: DCE = 1,2-dichloroethane, dppf = 1,1′-bis(diphenylphosphino)-ferrocene.

To complete the synthesis, allylic alcohol **12** was obtained from the 1,2-addition of vinylmagnesium bromide to **11**. Then, standard Suzuki−Miyaura conditions with isopropenyl boronic acid pinacol ester gave triene **13** in 59% yield.[16] The final two steps of the synthesis proved to be problematic. Triene **13** was found to be unstable under various oxidation conditions. (See the Supporting Information.) Eventually, it was found that the use of Dess−Martin periodinane with one equivalent of water gave good results. Without water, an allylic transposition product was observed in appreciable quantities.[17]

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For the Diels–Alder reaction, we investigated a number of different conditions spanning both thermal and Lewis-acid-promoted transformations. (See the Supporting Information.) Although the conditions reported by Baran and coworkers (3.65 equiv of $BF_3{\cdot}Et_2O$, slow addition at 0 °C)[2a] gave trace product (10% yield, 1:1 d.r., 92% ee), our substrate, being structurally different from that employed by Baran and coworkers, required extensive screening to reach an acceptable yield. The best results were obtained via the slow addition of the substrate to a dilute and cold (−35 °C) solution of the Lewis acid, which furnished **15** in 35% yield as a 1:1 mixture of diastereomers at C1 and 92% ee.

One might assume that quaternary stereocenter C8 is responsible for the stereoinduction at C1 and that the poor diastereoselectivity is a result of the remoteness of C8. In the Diels–Alder reaction to form **2**, Baran and coworkers observed a diastereomeric ratio of 2:1 (desired/undesired) at C3 in the cyclization precursor, which corresponded to an identical ratio at C1 in the product.[2a] While these centers are α to carbonyls, this may suggest that C3 is responsible for the diastereoselectivity, and we note that **14** lacks a C3 stereocenter.

In conclusion, the Taxol core was prepared in five steps from commercially available 3-methyl-2-cyclohex-2-ene-1-one **6** in 11% yield with 92% ee. The key step employed a hydrometalation ACA/trapping sequence of functionalized alkene **9** to furnish unsaturated β-chloroaldehyde **11** in high enantiomeric excess. Further elaboration of this intermediate to the ketone was accomplished via an addition, cross-coupling, and oxidation sequence. Finally, an intramolecular Diels–Alder reaction simultaneously formed the A and B rings to deliver the Taxol core. We believe that this work highlights the benefits of using organozirconium nucleophiles in asymmetric addition reactions for total synthesis and related applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01165.

All procedures, characterization data, NMR spectra, and chromatography traces (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Hudlicky, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, Germany, 2007. For syntheses of Taxol see: (b) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. First total synthesis of taxol. 2. Completion of the C and D Rings. *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600. (c) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. Total synthesis of taxol. *Nature* **1994**, *367*, 630–634. (d) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. Total synthesis of baccatin III and taxol. *J. Am. Chem. Soc.* **1996**, *118*, 2843–2859. (e) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. The pinene path to taxanes. 6. A concise stereocontrolled synthesis of taxol. *J. Am. Chem. Soc.* **1997**, *119*, 2757–2758. (f) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. Asymmetric total synthesis of Taxol. *Chem. - Eur. J.* **1999**, *5*, 121–161. (g) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. Enantioselective Total Synthesis of (−) − Taxol. *J. Am. Chem. Soc.* **2000**, *122*, 3811–3820. (h) Doi, T.; Fuse, S.; Miyamoto, S.; Nakai, K.; Sasuga, D.; Takahashi, T. A formal total synthesis of taxol aided by an automated synthesizer. *Chem. - Asian J.* **2006**, *1*, 370–383. (i) Hirai, S.; Utsugi, M.; Iwamoto, M.; Nakada, M. Formal total synthesis of (−)-taxol through Pd-catalyzed eight-membered carbocyclic ring formation. *Chem. - Eur. J.* **2015**, *21*, 355–359. (j) Fukaya, K.; Kodama, K.; Tanaka, Y.; Yamazaki, H.; Sugai, T.; Yamaguchi, Y.; Watanabe, A.; Oishi, T.; Sato, T.; Chida, N. Synthesis of paclitaxel. 2. construction of the ABCD ring and formal synthesis. *Org. Lett.* **2015**, *17*, 2574–2577.

(2) Synthesis of taxadiene and the two-phase approach of terpene synthesis: (a) Mendoza, A.; Ishihara, Y.; Baran, P. S. Scalable enantioselective total synthesis of taxanes. *Nat. Chem.* **2012**, *4*, 21–25. (b) Ishihara, Y.; Mendoza, A.; Baran, P. S. Total synthesis of taxane terpenes: Cyclase phase. *Tetrahedron* **2013**, *69*, 5685–5701. (c) Krasutsky, S. G.; Jacobo, S. H.; Tweedie, S. R.; Krishnamoorthy, R.; Filatov, A. S. Route optimization and synthesis of taxadienone. *Org. Process Res. Dev.* **2015**, *19*, 284–289. (d) Ishihara, Y.; Baran, P. S. Two-phase terpene total synthesis: Historical perspective and application to the Taxol problem. *Synlett* **2010**, *2010*, 1733–1745. (e) Kanda, Y.; Nakamura, H.; Umemiya, S.; Puthukanoori, R. K.; Appala, V. R. M.; Gaddamanugu, G. K.; Paraselli, B. R.; Baran, P. Two-Phase Synthesis of Taxol®. *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.12061620.v1.

(3) Selected examples of intramolecular Diels–Alder reactions used in taxane syntheses: (a) Sakan, K.; Craven, B. M. Synthetic Studies on the Taxane Diterpenes. Utility of the Intramolecular Diels-Alder Reaction for a Single-Step Stereocontrolled Synthesis of a Taxane Model System. *J. Am. Chem. Soc.* **1983**, *105*, 3732–3734. (b) Bonnert, R. V.; Jenkins, P. R. A Synthesis of an Alkylated Taxane Model System. *J. Chem. Soc., Perkin Trans. 1* **1989**, *1*, 413–418. (c) Yadav, J. S. Synthesis of antitumour agents. *Pure Appl. Chem.* **1993**, *65*, 1349–1356. (d) Winkler, J. D.; Kim, H. S.; Kim, S. A highly efficient synthesis of taxanes via the tandem Diels-Alder reaction. *Tetrahedron Lett.* **1995**, *36*, 687–690. (e) Rubenstein, S. M.; Williams, R. M. Studies on the Biosynthesis of Taxol: Total Synthesis of Taxa-4(20),11(12)-diene and Taxa-4(5),11(12)-diene. The First Committed Biosynthetic Intermediate. *J. Org. Chem.* **1995**, *60*, 7215–7223.

(f) Stec, M. M.; Gwaltney, S. L.; Burke, L. D.; Nguyen, H.; Shea, K. J. Stereoselective synthesis of an advanced taxusin intermediate: An application of the type 2 intramolecular Diels-Alder reaction. *Tetrahedron Lett.* **2003**, *44*, 9379−9382.
(4) Vuagnoux-D'Augustin, M.; Alexakis, A. Copper-catalyzed asymmetric conjugate addition of trialkylaluminium reagents to trisubstituted enones: Construction of chiral quaternary centers. *Chem. - Eur. J.* **2007**, *13*, 9647−9662.
(5) (a) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. Recent advances in enantioselective copper-catalyzed 1,4-addition. *Chem. Soc. Rev.* **2009**, *38*, 1039−1075. (b) Maksymowicz, R. M.; Bissette, A. J.; Fletcher, S. P. Asymmetric conjugate additions and allylic alkylations using nucleophiles generated by hydro- or carbometallation. *Chem. - Eur. J.* **2015**, *21*, 5668−5678.
(6) Asymmetric conjugate addition to form quaternary centers: (a) Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. Formation of quaternary centers by copper-catalyzed asymmetric conjugate addition of alkylzirconium reagents. *Angew. Chem., Int. Ed.* **2013**, *52*, 7995−7999. (b) Roth, P. M. C.; Sidera, M.; Maksymowicz, R. M.; Fletcher, S. P. Copper-catalyzed asymmetric conjugate addition of alkylzirconium reagents to cyclic enones to form quaternary centers. *Nat. Protoc.* **2014**, *9*, 104−111. Acyclic systems: (c) Gao, Z.; Fletcher, S. P. Acyclic quaternary centers from asymmetric conjugate addition of alkylzirconium reagents to linear trisubstituted enones. *Chem. Sci.* **2017**, *8*, 641−646. Five-membered rings: (d) Ardkhean, R.; Mortimore, M.; Paton, R. S.; Fletcher, S. P. Formation of quaternary centres by copper catalysed asymmetric conjugate addition to β-substituted cyclopentenones with the aid of a quantitative structure-selectivity relationship. *Chem. Sci.* **2018**, *9*, 2628−2632.
(7) Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. Catalytic asymmetric carbon−carbon bond formation using alkenes as alkylmetal equivalents. *Nat. Chem.* **2012**, *4*, 649−654.
(8) For the use of this approach in complex molecule synthesis, see: (a) Wu, J.; Kadonaga, Y.; Hong, B.; Wang, J.; Lei, X. Enantioselective Total Synthesis of (+)-Jungermatrobrunin A. *Angew. Chem., Int. Ed.* **2019**, *58*, 10879−10883. (b) Wang, J.; Hong, B.; Hu, D.; Kadonaga, Y.; Tang, R.; Lei, X. Protecting-Group-Free Syntheses of ent-Kaurane Diterpenoids: [3 + 2+1] Cycloaddition/Cycloalkenylation Approach. *J. Am. Chem. Soc.* **2020**, *142*, 2238−2243. (c) Caprioglio, D.; Fletcher, S. P. An alternative synthesis of the breast cancer drug fulvestrant (Faslodex®): catalyst control over C−C bond formation. *Chem. Commun.* **2015**, *51*, 14866−14868. (d) Garrec, K.; Fletcher, S. P. Cp2ZrMeCl: A Reagent for Asymmetric Methyl Addition. *Org. Lett.* **2016**, *18*, 3814−3817. (e) Gao, Z.; Fletcher, S. P. Asymmetric conjugate addition of alkylzirconium reagents to α,β-unsaturated thioesters: Access to fragrances and acyclic stereochemical arrays. *Chem. Commun.* **2017**, *53*, 10216−10219.
(9) Triene **5** was obtained in one step via Negishi cross-coupling of vinyl zinc bromide and bromodiene **8** in 49% yield. Bromodiene **8** precursor: (a) Jackson, R. W.; Shea, K. J. Synthesis of a C-1 epi taxinine intermediate using the type 2 intramolecular Diels-Alder approach. *Tetrahedron Lett.* **1994**, *35*, 1317−1320. (b) Magnus, P.; Westwood, N.; Spyvee, M.; Frost, C.; Linnane, P.; Tavares, F.; Lynch, V. Taxane diterpenes 5: Synthesis of the A- and C-rings: An unusual rearrangement of an N-hydroxyimino lactone. *Tetrahedron* **1999**, *55*, 6435−6452. (c) Laurent, A.; Villalva-Servín, N. P.; Forgione, P.; Wilson, P. D.; Smil, D. V.; Fallis, A. G. Part 1: Efficient strategies for the construction of variably substituted bicyclo[5.3.1]undecenones (AB taxane ring systems). *Can. J. Chem.* **2004**, *82*, 215−226.
(10) Ogasawara, M.; Ge, Y.; Uetake, K.; Fan, L.; Takahashi, T. Preparation of multisubstituted allenes from allylsilanes. *J. Org. Chem.* **2005**, *70*, 3871−3876.
(11) Gao, Z.; Fletcher, S. P. Construction of β to carbonyl stereogenic centres by asymmetric 1,4-addition of alkylzirconocenes to dienones and ynenones. *Chem. Commun.* **2018**, *54*, 3601−3604.
(12) Brethomé, A. V.; Paton, R. S.; Fletcher, S. P. Retooling Asymmetric Conjugate Additions for Sterically Demanding Substrates with an Iterative Data-Driven Approach. *ACS Catal.* **2019**, *9*, 7179−7187.
(13) Jacques, R.; Pullin, R. D. C.; Fletcher, S. P. Desymmetrization of meso-bisphosphates using copper catalysis and alkylzirconocene nucleophiles. *Nat. Commun.* **2019**, *10*, 1−6.
(14) (a) Némethová, I.; Sorádová, Z.; Šebesta, R. Electrophilic Trapping of Zirconium Enolates Obtained by Copper-Catalyzed Addition of In Situ Generated Organozirconium Reagents. *Synthesis* **2017**, *49*, 2461−2469. (b) Vargová, D.; Némethová, I.; Plevová, K.; Šebesta, R. Asymmetric Transition-Metal Catalysis in the Formation and Functionalization of Metal Enolates. *ACS Catal.* **2019**, *9*, 3104−3143.
(15) Wang, J. Y. J.; Palacin, T.; Fletcher, S. P. β-Chloroaldehydes from Trapping Zirconium Enolates Produced in Asymmetric 1,4-Additions. *Org. Lett.* **2019**, *21*, 378−381.
(16) The yields could not be improved, and we attributed this to the steric hindrance at the bromide.
(17) Luzzio, F. A. 1,3-Oxidative transpositions of allylic alcohols in organic synthesis. *Tetrahedron* **2012**, *68*, 5323−5339.

https://dx.doi.org/10.1021/acs.orglett.0c01165
Org. Lett. XXXX, XXX, XXX−XXX