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Enantioselective Organocatalytic Conjugate Addition in a Tandem Synthesis of δ-Substituted Cyclohexenones and Four-Step Total Synthesis of Penienone

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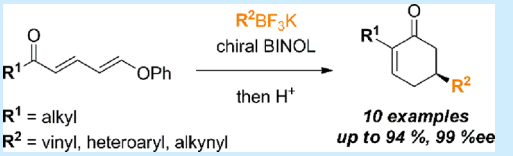
ABSTRACT: A bisperfluorotoluyl−BINOL catalyzed conjugate addition of trifluoroborate salts to doubly vinylogous esters and aldol condensation synthesized chiral δ-substituted cyclohexenones with high yields and enantioselectivities (10 examples, up to 89% yield, 89−98% ee). Stepwise and single-pot sequences were developed, with the former also providing β-substituted masked ketoaldehydes containing a vinyl ether. The transformation was used in a four-step total synthesis of penienone (24% overall yield), ≤ half the steps as in previous syntheses.



Cyclohexenone is a widely used synthetic building block[1] that also appears as a common motif in natural products and biologically active organic molecules.[2] A key elaboration of this motif is the addition of a δ-stereocenter to the cyclohexenone, where the enone functional group offers myriad transformations under the control of that stereocenter.[1] Previously, δ-substituted cyclohexenones have required many synthetic steps to enantioselectively synthesize due to the impossibility of generating the δ-stereocenter using an enantioselective conjugate addition to a doubly unsaturated cyclohexanone (boxed transformation in Scheme 1). Three recent advances have improved synthetic access to δ-substituted cyclohexenones. In 2008, the List group demonstrated an organocatalyzed intramolecular Aldol condensation from racemic diketones for chiral β-methyl, δ-substituted cyclohexenones (Scheme 1A).[3a] In 2015, the Rodriguez group reported the synergistic copper and chiral amine activated addition of 1,3-acetonedicarboxylic acid to cinnamaldehyde derivatives in a dinucleophilic Robinson annulation (Scheme 1B).[3b] In 2018, the Nagorny group then described examples of chiral Cu(II) catalyzed decarboxylative Robinson annulation after addition of β-ketocarboxylic acids to a ketone Michael acceptor (Scheme 1C).[3c] In each of these approaches, the R group at the δ-stereocenter must be preincorporated in the component pieces. Consequently, none of them allow facile variation of the R group as a discrete component in the synthesis, which decreases efficiency and prevents late-stage diversification. We were thus inspired to pursue a new enantioselective and metal-free conjugate addition/aldol condensation strategy to introduce this substituent in a modular fashion to maximize diversification of this building block, amplify efficiency, and minimize the effort needed to alter this key stereocenter. Moreover, this approach will allow exploration of novel and unusual reactivity based on vinylogous ester electrophiles.[4]

Potassium trifluoroborate salts are not exclusively used in transition metal couplings.[5] These salts are also widely used in nucleophilic addition with various electrophiles, such as Michael acceptors,[6] cyclopropane derivatives,[7] aziridines,[8] azetidines,[8] and epoxides.[9] Recently, our group developed a conjugate addition/elimination cascade reaction in a unique use of vinylogous esters as conjugate acceptors.[4] The Mao and Chang groups shortly thereafter reported the enantioselective 1,4-conjugate addition on a vinylogous amide to synthesize the corresponding amine.[10] In this report, we extend the vinylogous system by an additional alkenyl unit, with the corresponding doubly vinylogous ester being easily generated by nucleophilic addition to a terminal alkyne. We hypothesized that a BINOL-derived organocatalyst combined with trifluoroborate salts and the doubly vinylogous ester would give exclusively a 1,4-addition product rather than the alternative 1,6-addition product (Scheme 1D). The anticipated selectivity would be due to the tight, intramolecular delivery of the nucleophile from a strong Lewis acid/base complex formed between the BINOL-bound organoboronate and the doubly vinylogous ester.[11] This advance has enabled a novel strategy for us to synthesize δ-substituted cyclohexenones via enantioselective organocatalyzed 1,4-conjugate addition, followed by acid promoted aldol condensation.

The first stage of our strategy was dependent on an efficient and enantioselective conjugate addition to an extended vinylogous ester **1a**. We began our tests with the potassium salt of styrenyl trifluoroborate as a nucleophile in the presence of 3,3′-bisperfluorotoluyl-BINOL, which has routinely been the most effective catalyst for such enantioselective conjugate additions, and 4 Å molecular sieves (Table 1, entry 1). To our delight, the 1,4-addition product **2a** was formed, albeit in 21%

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Scheme 1. Enantioselective Approaches to δ-Substituted Cyclohexenones

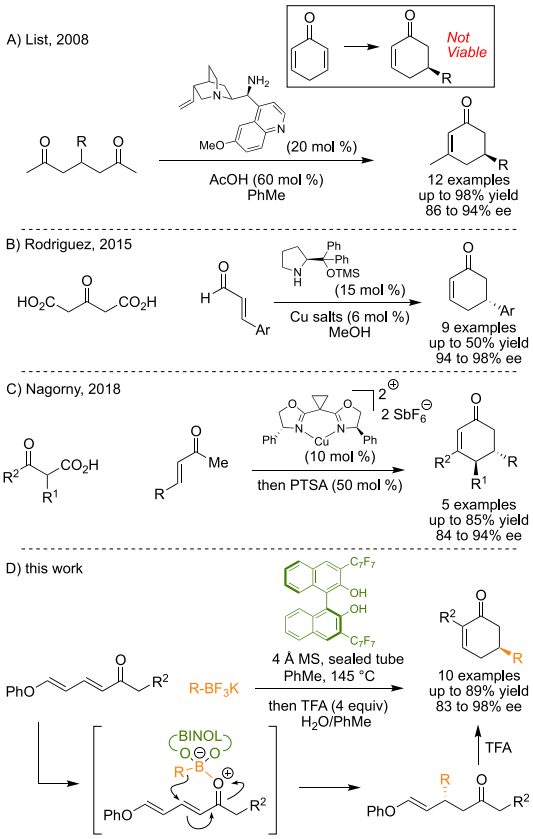
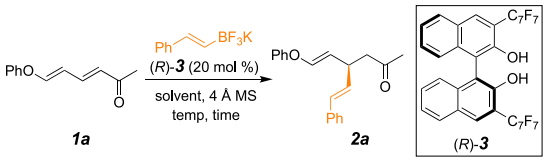


Table 1. Optimization of the Conjugate Addition

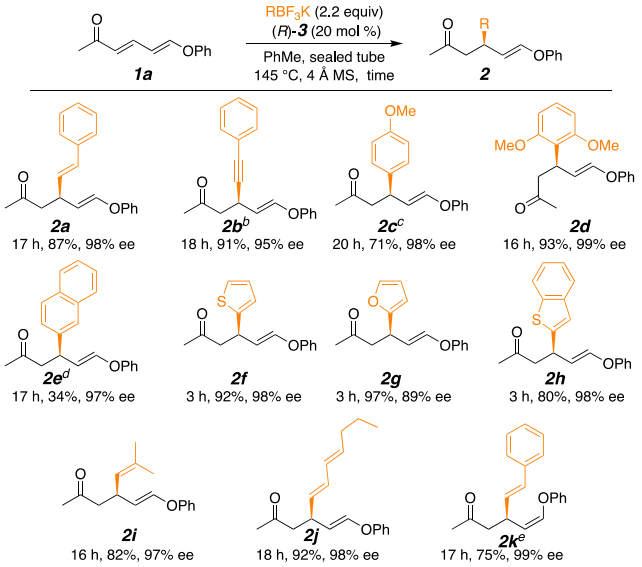


entry	RBF_3K (equiv)	solvent	temp (°C)	time (h)	yield (%)[a]
1	1.5	PhMe	70	72	21
2	1.5	MeCN	reflux	48	<5
3	1.5	1,4-dioxane	100	48	17
4	1.5	PhMe	100	48	43
5	1.5	PhMe	reflux	48	63[b]
6	1.5	PhCl	reflux	43	77
7	1.5	*p*-xylene	reflux	17	76[c]
8[d]	1.5	PhMe	145	17	87[c]
9[d]	2.2	PhMe	145	17	85[c]
10[d,e]	2.2	PhMe	145	17	0

[a]Isolated yields. [b]**1a** was recovered in 34% yield. [c]3,3′−bisperfluorotoluyl−BINOL was used as catalyst, 98% ee determined by HPLC with chiral stationary phase. [d]The reaction was performed in a sealed tube. [e]Boronic acid was used.

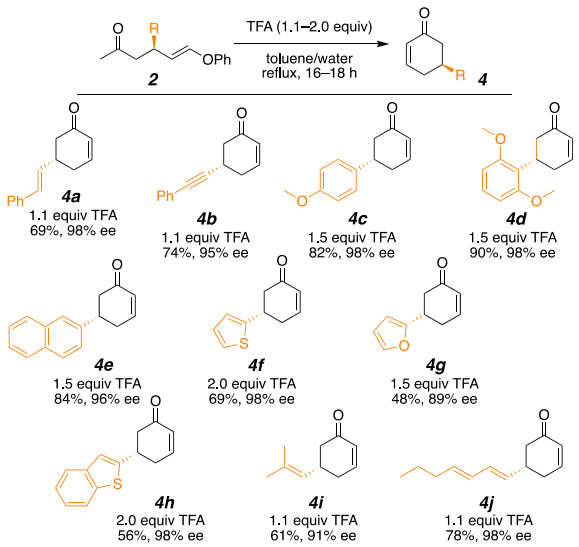
yield. As has been observed previously,[4,6−8] polar solvents such as acetonitrile inhibited the reaction, as did 1,4-dioxane (entries 2 and 3). Increasing the reaction temperature from 70 °C in toluene to 100 °C or reflux gave a 43% and 63% yield, respectively (entries 4 and 5). It is worth noting the starting material was recovered from the reflux conditions in 34% yield without any decomposition. This result inspired examination

Scheme 2. Substrate Scope of Conjugate Product[a]



[a]Isolated yield. Determined ee using HPLC with chiral stationary phase. [b]With 3.0 equiv of potassium trifluoroborate (2.2 equiv gave 76%, 97% ee in 21 h). [c]With 3.0 equiv of potassium trifluoroborate (2.2 equiv gave 62%, 98% ee in 20 h). [d]With 3.0 equiv of potassium trifluoroborate. [d](*E*,*Z*)-**1a** was used as a starting material. [e](*Z*)-**1a** was used as a starting material.

Scheme 3. Enantioselective Synthesis of δ-Substituted Cyclohexenone[a]



[a]All products were isolated and enantioselective excess were determined by HPLC with chiral stationary phase.

of a higher boiling solvent. In chlorobenzene and *p*-xylene, the product yields were 77% and 76%, respectively (entries 6 and 7). Moreover, the higher boiling solvent, *p*-xylene, shortened the reaction time from 48 to 17 h while maintaining high enantioselectivity (see footnote c).[6a] We desired to see if the more accessible solvent, toluene, could reproduce the yields from *p*-xylene at higher temperatures. Fortunately, the use of toluene in a sealed tube heated to 145 °C gave the best yield (entry 8). Control experiments using a boronic acid instead of the potassium trifluoroborate resulted in nonspecific decomposition of **1a** (entry 10).

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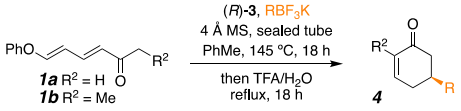
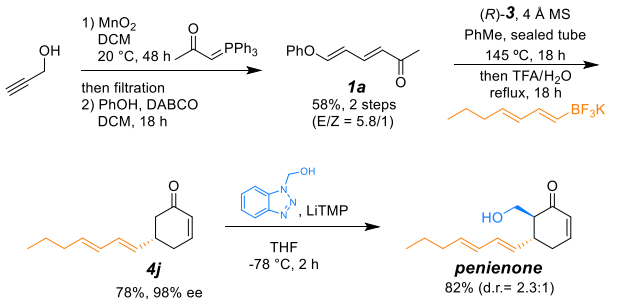
Table 2. Single Reaction Synthesis of δ-Substituted Cyclohexenones



entry	R	R^2	product	yield (%)[a]	% ee[b]
1	(*E*)-styryl	H	**4a**	85	98
2	(*E*)-styryl	Me	**4k**	37	99
3	2-phenylethynyl	H	**4b**	60	94
4	4-methoxyphenyl	H	**4c**	70	98
5	2,6-dimethoxyphenyl	H	**4d**	89	98
6	2-thienyl	H	**4f**	53	98
7	2-furyl	H	**4g**	58	83
8	2-benzo[*b*]thienyl	H	**4h**	60	98
9	2-methylpropenyl	H	**4i**	decomposed	N.D.[c]
10	(1*E*,3*E*)-1,3-heptadienyl-	H	**4j**	78	98

[a]Isolated yield, average of 2 trials. [b]Determined by HPLC with chiral stationary phase. [c]N.D. = Not Determined.

Scheme 4. Synthesis of (+)-penienone



With effective conditions for the first stage of our strategy in hand, the versatility of the reaction was further tested by using an array of nucleophiles (Scheme 2). An alkynyl trifluoroborate salt was incorporated in good yield, though with a slightly lower 95% ee (**2b**). For an aromatic trifluoroborate salt, an electron-donating group was needed to have sufficient reactivity for the conjugate addition. Potassium 4-methoxyphenylborate, for example, generated the arylated ketone **2c** in a useful yield. Increasing the amount of the borate salt to 3.0 equiv improved the yield. Including sterically encumbering *ortho*-substitution on an aromatic nucleophile did not impede the reaction, and product formation was still observed in good yield (**2d**). Unsubstituted and electron-poor phenyl rings gave no reaction. Nevertheless, a naphthyl nucleophile gave adduct **2e** in 34% yield. Apparently, reduced aromatic stabilization and electronic donating groups facilitated C−C bond formation. Moreover, heteroaromatic trifluoroborates gave good yields with short reaction times due to their strong nucleophilicity (**2f**−**2h**). While 1.5 equiv of the thienyl trifluoroborate salt gave the product **2f** in a low yield, presumably due to facile protodeboronation, using 2.2 equiv gave **2f** in 92% yield. For the furyl product **2g**, the stereoselectivity was the lowest observed, but it was still synthetically useful. A dimethyl vinyl nucleophile provided the product **2i** in 82% yield, though a linear alkene was not viable.[12] It is proposed that there is significant positive charge build-up at the nucleophilic carbon during C−C bond formation,[11b−d] and we hypothesized that secondary carbocation character in the intermediate from a linear nucleophile is not stabilized enough for a facile reaction. This hypothesis prompted the testing of a dienyl nucleophile, which would generate a more stabilized allylic cation during C−C bond formation, to overcome this problem. Accordingly, the dienyl product **2j** was formed in 92% yield. Lastly, the stereochemistry of the vinyl ether had only a minor impact on the reaction (compare **2a** and **2k**), so either the *E* or *Z* vinylogous ester could be used. It is also notable that the vinyl ether stereochemistry was unchanged in the reaction.

Next, the second stage of our strategy, the acid promoted Aldol condensation, was tested. Adduct **2a** was chosen as a model to see the effects of various Brønsted acids.[12] The aldehyde that would have formed from hydrolysis of the enol ether was not observed. Instead, the direct aldol condensation proceeded, and the δ-substituted cyclohexenone **4a** was formed in moderate yield with no loss of enantioenrichment at the chiral center when using TFA (Scheme 3). Some acids like *p*-TsOH or HCl were found to decompose some substrates.[12] TFA was found to be the most general reagent for a variety of substrates that formed cyclohexenones **4a**−**j**. The equivalents of TFA could be optimized for improved yields of individual substrates. Both styrenyl and phenylethynyl substituents were tolerant of the acidic conditions, providing cyclohexenones **4a** and **4b**, respectively, in good yields and ≥95% ee. The aromatic substituents gave higher yields (**4c**−**4e**). Even though the heteroaromatic groups incorporated in **2f**, **2g**, and **2h** provided good reactivity for the conjugate addition, long reaction times in the presence of acid gave lower yields for **4f**−**4h**, presumably due to the acid sensitivity of the heterocycles. Changing the acid usually caused decomposition or oxidation of the product, producing substituted phenols. Notably, the monoterpenoid-like frameworks in **4i** and **4j** can be useful synthetic building blocks. For example, the dienyl ketone **4j** is a precursor of the natural product penienone.[13]

Next, the culmination of our strategy was to combine these two steps into a single reaction by adding 4.0 equiv of TFA to the reaction solution to promote the aldol condensation once the conjugate addition was completed (Table 2). Cyclohexenones were thus obtained in high yields and enantioselectivities in a single reaction. The (*E*)-styrenyl and alkynyl substituted **4a** and **4b** were formed in 85% and 60% yield, respectively (entries 1 and 3). The ethyl ketone in doubly vinylogous ester **1b** was compatible with this method, synthesizing the methylated cyclohexenone **4k** in 37% yield (entry 2). Acid-tolerant groups like the aromatic substituents gave the best yields (entries 4−5). But acid-sensitive substituents like the heteroaromatics gave slightly lower yields

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(entries 6−8). The highly sensitive dimethyl vinyl in the monoterpene-like **4i**, however, resulted in decomposition.

The greatly increased efficiency from this innovative strategy resulted in a novel synthesis of penienone. Sato,[14a] Myers,[14b] and Nanda[14c] reported syntheses of this natural product previously. However, their strategies to access the key intermediate **4j** required 8 to 14 steps (10 to 17 steps for the total syntheses, 7.5−19% overall yield). In contrast, the rapid strategy presented herein produced **4j** in only 3 total reactions with high yields and 98% ee (Table 2, entry 10 and Scheme 4). Using a masked formaldehyde precursor,[15] 1*H*-benzotriazole-1-ethanol, and 3.0 equiv of LiTMP with **4j** gave penienone successfully with its diastereomer in 80% combined yield.

In conclusion, the synthesis of chiral δ-substituted cyclohexenones has been greatly expedited via 3,3′-perfluorotoluyl-BINOL catalyzed enantioselective conjugate addition followed by aldol condensation, either as two separate reactions or as a single reaction. Both approaches provided products in good to high yields and high ee's. Furthermore, the total synthesis of the natural product, penienone, was accomplished in 4 steps in 43% overall yield and 98% ee from commercially available propargyl alcohol. Additional synthetic efforts that take advantage of this privileged building block are now underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01976.

Completed experimental procedures and compound characterization data are provided. (PDF)

Accession Codes

CCDC 2121713 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

P.-K.P.: Investigation, data acquisition, writing−original draft, conceptualization. J.A.M.: Funding acquisition, project administration, writing−review and editing, conceptualization.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Yang, X.; Wang, J.; Li, P. recent progress on asymmetric organocatalytic construction of chiral cyclohexenone skeletons. *Org. Biomol. Chem.* **2014**, *12*, 2499−2513. (b) Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. The concept of transient chirality in the stereoselective synthesis of functionalized cycloalkenes applying the retro-Diels−Alder methodology. *Chem. Rev.* **1999**, *99*, 1163−1190. (c) Sato, F.; Urabe, H.; Okamoto, S. Synthesis of organotitanium complexes from alkenes and alkynes and their synthetic applications. *Chem. Rev.* **2000**, *100*, 2835−2886.

(2) For selected reviews, see: (a) Strack, D.; Fester, T. Isoprenoid metabolism and plastid reorganization in arbuscular mycorrhizal roots. *New Phytol.* **2006**, *172*, 22−34. (b) Akiyama, K. Chemical identification and functional analysis of apocarotenoids involved in the development of arbuscular mycorrhizal symbiosis. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 1405−1414.

(3) (a) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. Primary-amine-catalyzed enantioselective intramolecular aldolizations. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656−7658. (b) Quintard, A.; Rodriguez, J. Synergistic Cu−amine catalysis for the enantioselective synthesis of chiral cyclohexenones. *Chem. Commun.* **2015**, *51*, 9523−9526. (c) Lee, J.; Wang, S.; Callahan, M.; Nagorny, P. Copper(II)-catalyzed tandem decarboxylative michael/aldol reactions leading to the formation of functionalized cyclohexenones. *Org. Lett.* **2018**, *20*, 2067−2070. (d) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. A simple asymmetric organocatalytic approach to optically active cyclohexenones. *Chem. Commun.* **2006**, 4928−4930.

(4) Sundstrom, S.; Nguyen, T. S.; May, J. A. Relay catalysis to synthesize β-substituted enones: organocatalytic substitution of vinylogous esters and amides with organoboronates. *Org. Lett.* **2020**, *22*, 1355−1359.

(5) (a) Molander, G. A.; Ellis, N. Organotrifluoroborates: protected boronic acids that expand the versatility of the suzuki coupling reaction. *Acc. Chem. Res.* **2007**, *40*, 275−286. (b) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of boron reagents for Suzuki−Miyaura coupling. *Chem. Soc. Rev.* **2014**, *43*, 412−443.

(6) (a) Shih, J.-L.; Nguyen, T. S.; May, J. A. Organocatalyzed asymmetric conjugate addition of heteroaryl and aryl trifluoroborates: a synthetic strategy for discoipyrrole D. *Angew. Chem., Int. Ed.* **2015**, *54*, 9931−9935. (b) Nguyen, T. N.; May, J. A. Enantioselective organocatalytic conjugate addition of organoboron nucleophiles. *Tetrahedron Lett.* **2017**, *58*, 1535−1544.

(7) Nguyen, T. N.; May, J. A. Tertiary and quaternary carbon formation via gallium-catalyzed nucleophilic addition of organoboronates to cyclopropanes. *Org. Lett.* **2018**, *20*, 112−115.

(8) Nguyen, T. N.; May, J. A. Branched amine synthesis via aziridine or azetidine opening with organotrifluoroborates by cooperative Brønsted/Lewis acid catalysis: an acid-dependent divergent mechanism. *Org. Lett.* **2018**, *20*, 3618−3621.

(9) (a) Roscales, S.; Csákÿ, A. G. Metal-free ring-opening of epoxides with potassium trifluoroborates. *Chem. Commun.* **2014**, *50*, 454−456. (b) Roscales, S.; Csákÿ, A. G. Transition-metal-free C−C bond forming reactions of aryl, alkenyl and alkynylboronic acids and their derivatives. *Chem. Soc. Rev.* **2014**, *43*, 8215−8225.

(10) (a) Wang, J.-F.; Meng, X.; Zhang, C.-H.; Yu, C.-M.; Mao, B. Organocatalytic enantioselective conjugate alkynylation of β-amino-enones: access to chiral β-alkynyl-β-amino carbonyl derivatives. *Org. Lett.* **2020**, *22*, 7427−7432. (b) Yao, E.-Z.; Chai, G.-L.; Zhang, P.; Zhu, B.; Chang, J. Chiral dihydroxytetraphenylene-catalyzed enantioselective conjugate addition of boronic acids to β-enaminones. *Org. Chem. Front.* **2022**, *9*, 2375−2381.

(11) (a) Turner, H. M.; Patel, J.; Niljianskul, N.; Chong, J. M. Binaphthol-catalyzed asymmetric conjugate arylboration of enones.

Org. Lett. **2011**, *13*, 5796−5799. (b) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. Theoretical study of the asymmetric conjugate alkenylation of enones catalyzed by binaphthols. *J. Org. Chem.* **2008**, *73*, 5078−5089. (c) Pellegrinet, S. C.; Goodman, J. M. Asymmetric conjugate addition of alkynylboronates to enones: rationale for the intriguing catalysis exerted by binaphthols. *J. Am. Chem. Soc.* **2006**, *128*, 3116−3117. (d) Simonetti, S. O.; Pellegrinet, S. C. Asymmetric organocatalytic c-c bond forming reactions with organoboron compounds: a mechanistic survey. *Eur. J. Org. Chem.* **2019**, *2019*, 2956−2970.

(12) For full experimental details, see Supporting Information.

(13) Kimura, Y.; Mizuno, T.; Shimada, A. Penienone and penihydrone, new plant growth regulators produced by the fungus, Penicillium sp. No.13. *Tetrahedron Lett.* **1997**, *38*, 469−472.

(14) (a) Hareau, G. P. J.; Koiwa, M.; Hikichi, S.; Sato, F. Synthesis of optically active 5-(tert-butyldimethylsiloxy)-2-cyclohexenone and its 6-substituted derivatives as useful chiral building blocks for the synthesis of cyclohexane rings. Syntheses of carvone, penienone, and penihydrone. *J. Am. Chem. Soc.* **1999**, *121*, 3640−3650. (b) Waterson, A. G.; Meyers, A. I. Bicyclic lactams as chiral homoenolate equivalents: synthesis of (−)-penienone. *J. Org. Chem.* **2000**, *65*, 7240−7243. (c) Mahapatra, T.; Bhunya, R.; Nanda, S. Chemo-enzymatic asymmetric total synthesis of penienone. *Tetrahedron Lett.* **2009**, *50*, 5392−5394.

(15) Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. Anionic, in situ generation of formaldehyde: a very useful and versatile tool in synthesis. *Org. Lett.* **2007**, *9*, 1165−1167.

https://doi.org/10.1021/acs.orglett.2c01976
Org. Lett. XXXX, XXX, XXX−XXX