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Catalytic Enantioselective Allylation of Acetylenic Aldehydes by Chiral Phosphoric Acid/Transition Metal Cooperative Catalysis: Formal Synthesis of Fostriecin

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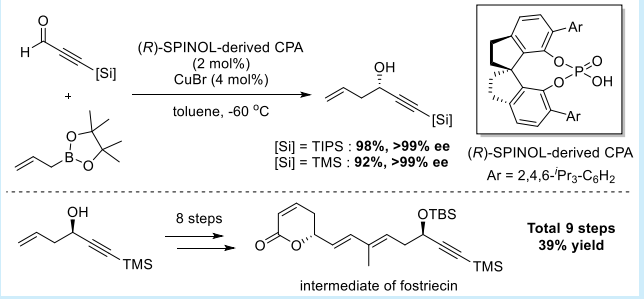
ABSTRACT: An enantioselective allylation of silyl-substituted acetylenic aldehydes by chiral phosphoric acid (CPA)/transition metal cooperative catalysis was developed. Enantioenriched homoallylic propargyl alcohols were obtained in good yields with excellent enantioselectivities (>99% ee) under mild conditions. Moreover, the shortest formal synthesis of fostriecin was achieved by the present enantioselective allylation protocol as the key step. The known intermediate of fostriecin reported by McDonald and co-worker was synthesized in only nine steps in 39% total yield.



Optically active propargyl alcohols are useful building blocks for the synthesis of natural products and pharmaceuticals, as the alkyne moiety can be converted into various functional groups.[1] In particular, propargyl alcohol **A** synthesized by the asymmetric allylation of silyl-substituted acetylenic aldehydes is a valuable synthetic intermediate for the construction of complex molecules (Figure 1a).[2] Indeed, numerous total syntheses of natural products have been reported using enantioenriched alcohol **A** as the key intermediate (Figure 1b, highlighted in red). The development of reactions to produce homoallylic propargyl alcohol **A** in an enantioenriched form is an important task in synthetic organic chemistry because an efficient supply of this intermediate would facilitate the syntheses of complex molecules.

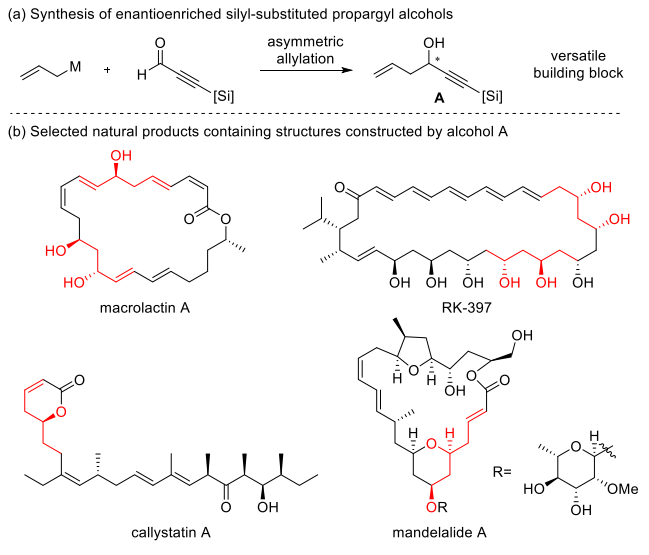


Figure 1. Synthetic utility of enantioenriched silyl-substituted propargyl alcohols.

Asymmetric allylation reactions using stoichiometric chiral reagents generated from chiral ligands and allylic metal species are widely utilized in the synthesis of natural products. Although these reactions are reliable, as they afford the desired product with high enantioselectivity, these reactions always require expensive chiral sources stoichiometrically and the use of water-sensitive reagents, thereby limiting utility and increasing difficulty in handling. The catalytic enantioselective allylation reactions of acetylenic aldehydes have attracted much attention in terms of green chemistry.[3] Hall and co-workers reported an enantioselective allylation of TMS-substituted acetylenic aldehyde in the presence of a chiral catalyst generated by $SnCl_2$ and chiral diol F-vivol-8 (Scheme 1, eq 1).[4a] Carter and co-workers achieved a total synthesis of mandelalide A by using the Keck allylation protocol that provides enantioenriched TMS-substituted propargyl alcohols (Scheme 1, eq 2).[4b] Although these two reactions are attractive synthetic tools, there is still room for improvement regarding enantioselectivity.

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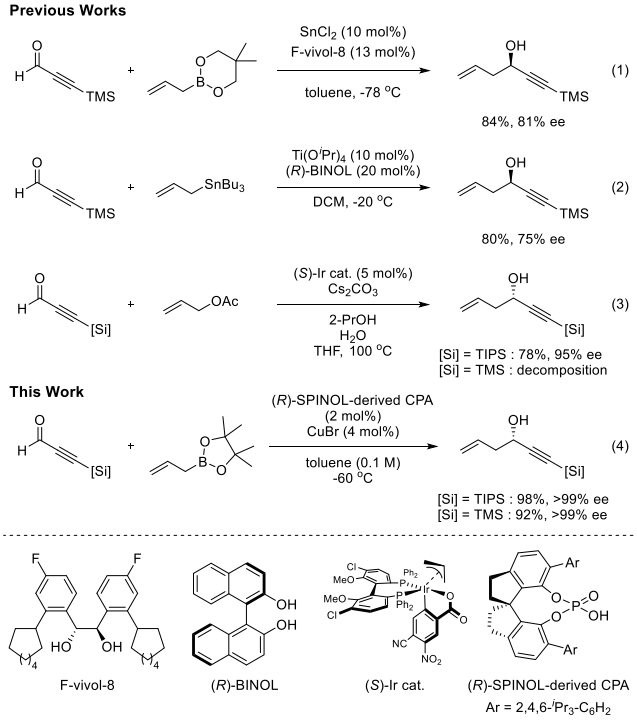
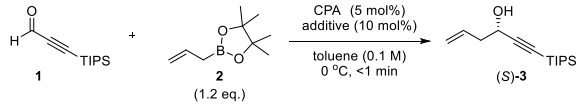
Scheme 1. Catalytic Enantioselective Allylation of Silyl-Substituted Acetylenic Aldehydes



Recently, Krische and co-workers reported an excellent method that generated TIPS-substituted homoallylic propargyl alcohols via an enantioselective Ir-catalyzed reductive coupling (Scheme 1, eq 3).[4c] They successfully obtained the desired allylation product in good yield with excellent enantioselectivity from an acetylenic aldehyde and an allyl acetate in the presence of an Ir catalyst they themselves developed. This is one of the most useful allylation reactions in modern organic synthesis. However, the TMS-substituted acetylenic aldehyde decomposed under the reaction conditions. A TMS-substituted triple bond is a convenient functional group for the synthesis of complex molecules because the TMS group can be easily and selectively deprotected under mild conditions, in contrast to common silyl protective groups, such as TES and TBS, of alcohols, which remain intact.[5] Herein we report an enantioselective allylation of TMS-substituted acetylenic aldehyde by a chiral phosphoric acid (CPA)/transition metal cooperative catalyst system (Scheme 1, eq 4) and a concise formal synthesis of fostriecin.

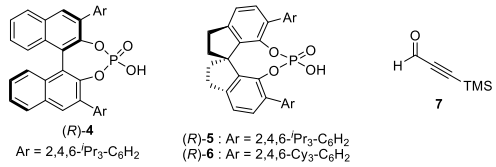
To determine the optimum conditions for the enantioselective allylation of acetylenic aldehyde, TIPS-substituted acetylenic aldehyde **1** was selected as the model substrate. Aldehyde **1** was reacted with allylboronic acid pinacol ester **2** immediately at 0 °C in the presence of 1,1′-bi-2-naphthol (BINOL)-derived CPA (*R*)-**4** (Ar = 2,4,6-^{i}Pr$_3$-C$_6$H$_2$),[6,7] which was reported as the best catalyst in Antilla's allylation conditions.[8] Substrate **1** was consumed within 1 min to afford desired product (*R*)-**3** in excellent yield but with low enantioselectivity (Table 1, entry 1). Next, 1,1′-spirobiindane-7,7′-diol (SPINOL)-derived CPA (*R*)-**5** (Ar = 2,4,6-^{i}Pr$_3$-C$_6$H$_2$) was employed for the reaction, as Hu and co-workers reported that catalyst **5** is very effective for the enantioselective allylation of aldehydes including Ph- and alkyl-substituted acetylenic aldehyde.[9] The catalyst was also found to be effective for the enantioselective allylation of the TIPS-substituted acetylenic aldehyde, giving allylation product (*S*)-**3** in excellent yield albeit with moderate enantioselectivity.[10] A series of transition metals that are allowed to coordinate to the triple bond of aldehyde **1** were evaluated, as shown in Table 1, entries 3 to 10. Fortunately, when CuBr was used as the additive, enantioselectivity was improved from 73% ee to 86% ee. A similar cooperative effect was observed when CuI was used, forming the desired product with good enantioselectivity (entry 4). Interestingly, no positive effect was observed when CuTC or [CuOTf]$_2$·PhMe was used, affording (*S*)-**3** with only 36% ee or 74% ee, respectively (entries 5 and 6). Experiments performed with Ag(I), Bi(III), Rh(II), and Pt(II) additives revealed that these metal species have no cooperative effect in the present enantioselective allylation reaction (entries 7 to 10). SPINOL-type catalyst (*R*)-**6** (Ar = 2,4,6-Cy$_3$-C$_6$H$_2$) gave a product with lower enantioselectivity than (*R*)-**5** (entry 11 vs entry 2). Finally, the reaction was performed at −60 °C in the CPA/CuBr cooperative catalyst system using (*R*)-**5** to furnish the product in 98% yield with excellent enantioselectivity (>99% ee) (entry 12). In the case of no additives, a lower enantioselectivity (96% ee) was observed than that of the cooperative system (entry 13 vs 12). These results clearly reveal that the combination of (*R*)-**5** and CuBr is effective to enhance the enantioselectivity in the present allylation reaction even under low temperature conditions.[11] With the optimal conditions in hand, TMS-substituted acetylenic aldehyde **7** was employed in the reaction with allylboronic acid **2** under these conditions. As expected, the desired product was obtained in 92% yield with >99% ee without any detrimental effect such as decomposition of substrate (entry 14).

Table 1. Optimization of Reaction Conditions[a]



entry	CPA	additives	yield/%[b]	ee/%[c]
1	(*R*)-**4**	none	93	−26[d]
2	(*R*)-**5**	none	95	73[e]
3	(*R*)-**5**	CuBr	99	86
4	(*R*)-**5**	CuI	98	80
5	(*R*)-**5**	CuTC	93	36
6	(*R*)-**5**	[CuOTf]$_2$·PhMe	95	74
7	(*R*)-**5**	AgOBz	90	−4
8	(*R*)-**5**	Bi(OAc)$_3$	96	58
9	(*R*)-**5**	Rh$_2$(OAc)$_4$	94	66
10	(*R*)-**5**	PtCl$_2$(PPh$_3$)$_2$	96	64
11	(*R*)-**6**	none	99	60
12[f]	(*R*)-**5**	CuBr	98	>99
13[f]	(*R*)-**5**	none	97	96
14[f,g]	(*R*)-**5**	CuBr	92	>99

[a]Unless otherwise noted, all reactions were carried out using 0.20 mmol of **1**, 0.24 mmol of **2**, and 0.010 mmol of CPA catalyst (5 mol %) in toluene. [b]Isolated yield. [c]Enantiomeric excess was determined by chiral stationary phase HPLC analysis. [d](*R*)-**3** was obtained. [e](*S*)-**3** was obtained. [f]The reaction was performed at −60 °C for 24 h. [g]Aldehyde **7** was employed.



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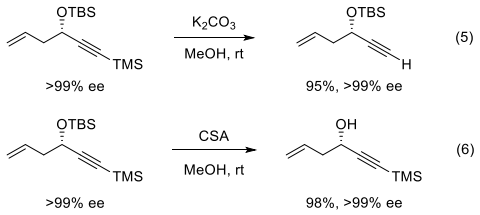
Previously, an enantio- and diastereoselective aldol reaction of acetylenic aldehydes catalyzed by the organocatalyst−transition metal−Brønsted acid cooperative system was reported by Palomo's group.[12] They concluded that the improvement of diastereoselectivity in the asymmetric aldol reaction would be explained by the steric inflation of the alkyne moiety by virtue of metal−alkyne association. In our case, CuBr would associate with the alkyne moiety of the aldehyde, resulting in increased steric hindrance.[13] Hence, the alkyne substituent tends to occupy the equatorial position in the six-membered transition state to enhance the enantioselectivity,[14] because the transition state giving the minor enantiomer would be destabilized due to steric congestion.

Next, the utility of the allylation product derived from TMS-substituted acetylenic aldehyde **7** is illustrated by selective deprotection of the silyl group under basic or acidic conditions (Scheme 2). The TMS group on the triple bond could be

Scheme 2. Selective Deprotection of Silyl Groups



removed selectively in the presence of the secondary TBS ether under mild basic conditions (Scheme 2, eq 5). On the other hand, the secondary TBS ether was converted into the corresponding alcohol under the 10-camphorsulfonic acid (CSA)/MeOH condition without loss of the TMS group attached to the triple bond terminus (Scheme 2, eq 6). During the course of these desilylation reactions, the enantiomeric purity remained unchanged.[15] These selective removal conditions highlight that the TMS-substituted propargyl alcohol should be useful in the late-stage functionalization of complex molecules.

Subsequent to the development of a highly enantioselective allylation of TMS-substituted acetylenic aldehyde **7**, we embarked on an investigation of a concise and efficient synthesis of fostriecin (CI-920), a phosphorylated polyketide (Figure 2). Fostriecin is a metabolite produced by Streptomyces pulveraceus isolated from a Brazilian soil sample.[16] Fostriecin and related natural products are considered to be an important class of compounds that

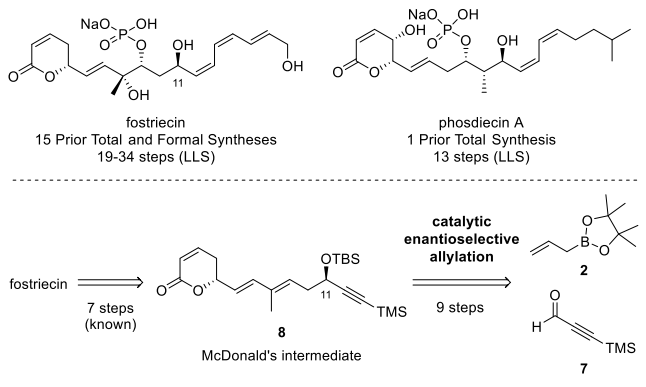


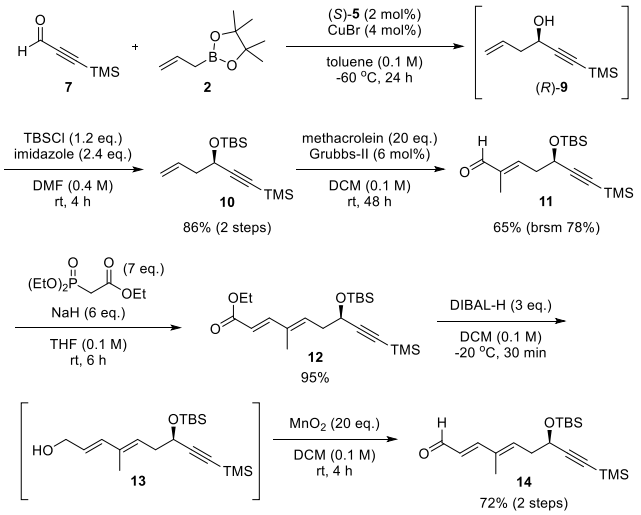
Figure 2. Synthetic plan of fostriecin via enantioselective allylation.

possess potent biological activities against leukemia, lung, breast, and ovarian cancer cells.[17] Fostriecin shows potent and selective inhibition of certain serine/threonine protein phosphatases, such as PP2A (IC_{50} 1.5 nM) and PP4 (IC_{50} 3 nM). Unfortunately, the use of fostriecin as a drug has been hindered by its chemical instability and the inconsistent purity of the compound derived from natural sources.[18] Thomasi and co-workers reported the isolation of two new phosphorylated natural products, phosdiecins A and B.[19] Krische and co-workers achieved the first total synthesis of phosdiecin A via an enantioselective carbonyl reductive coupling to validate the initial structure proposed by Thomasi and to explore the biological properties of this natural product.[20] Hence, the development of synthetic strategies for fostriecin and related compounds is valuable, as it would provide the desired product and new analogs in good purity and sufficient quantity.[21]

In 2009, McDonald and co-worker reported an elegant total synthesis of fostriecin via a convergent synthetic strategy.[22] We imagined that McDonald's intermediate **8** would be a key structure to provide fostriecin in a short and efficient manner (Figure 2). Indeed, **8** can be converted into the final product in only seven steps. Our synthetic plan is shown in Figure 2. The homoallylic propargyl alcohol moiety embedded in **8** would be synthesized via an enantioselective allylation of boronate **2** with aldehyde **7** in the CPA/CuBr cooperative catalyst system, in which enantiomeric (*S*)-**5** was employed to construct the stereochemistry at C11.

The present enantioselective allylation reaction of TMS-substituted acetylenic aldehyde **7** with allylboronic ester **2** was conducted under the optimal conditions to give desired homoallylic alcohol (*R*)-**9** with excellent enantioselectivity (Scheme 3). It is noteworthy that the allylation smoothly

Scheme 3. Enantioselective Synthesis of Intermediate 14



proceeded in the presence of only 2 mol % of (*S*)-**5** and 4 mol % of CuBr. The successive TBS protection of the secondary alcohol gave TBS ether **10** in 86% yield in two steps. Olefin cross metathesis catalyzed by Grubbs-II catalyst between **10** and methacrolein afforded corresponding α,β-unsaturated aldehyde **11** in 65% yield with recovery of substrate **10** in 20% yield (78% brsm).[23] The obtained aldehyde was subjected to the Horner−Wadsworth−Emmons reaction to furnish α,β−γ,δ-unsaturated ester **12** in 95% yield.[24] Reduction of ester **12** using DIBAL-H followed by oxidation of generated

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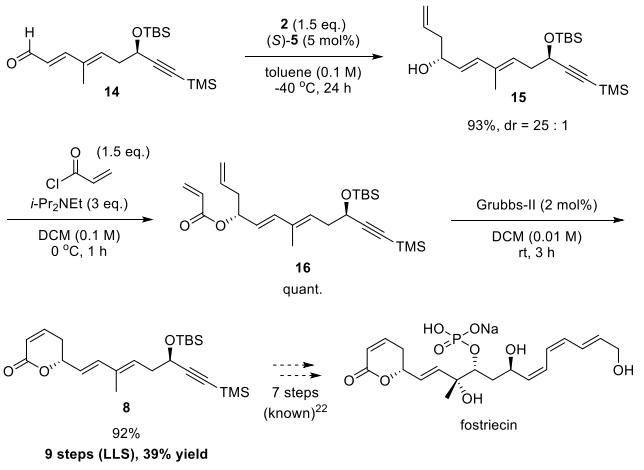
allylic alcohol **13** by MnO_2 delivered $\alpha,\beta-\gamma,\delta$-unsaturated aldehyde **14** in 72% yield in two steps.

Next, aldehyde **14** was treated with allylboronic acid pinacol ester **2** in the presence of (*S*)-**5** to give allylation product **15** in 93% yield with excellent diastereoselectivity (Scheme 4).[9,25]

Scheme 4. Formal Synthesis of Fostriecin



The newly generated alcohol was protected with acryloyl chloride followed by ring closing metathesis using Grubbs-II catalyst to construct a six-membered lactone.[26] McDonald's intermediate **8** was prepared in 39% total yield in nine steps from commercially available TMS-substituted acetylenic aldehyde through enantioselective allylations catalyzed by CPA. Our synthetic route can eliminate nine steps in total sequences and dramatically improve the total yield compared with McDonald's synthesis (a total of 18 steps, 18.4% yield). To date, 15 total and formal syntheses of fostriecin have been reported, which range from 19 to 34 steps (longest linear sequence (LLS)).[20] Our synthetic strategy is able to supply the targeted molecule in 16 steps theoretically.

In summary, we have developed an enantioselective allylation of silyl-substituted acetylenic aldehydes by using the CPA/CuBr cooperative catalyst system under mild conditions. Enantioenriched homoallylic propargyl alcohols, considered as versatile chiral building blocks, were readily obtained in excellent yields with perfect enantioselectivities. The selective desilylation protocols of the corresponding TMS-substituted propargyl silyl ether were demonstrated in terms of synthetic utility. Additionally, the formal synthesis of fostriecin was achieved by using the present enantioselective allylation as the key step. In our synthetic route, the known intermediate of fostriecin can be synthesized in only nine steps in 39% yield. This is the shortest formal synthesis of fostriecin, which is accomplished in 16 steps (LLS). The synthetic methodology and strategy can be utilized to provide not only related compounds of fostriecin but also other natural products in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01166.

Experimental procedure and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The absolute configuration of **3** was determined by comparison with the reported specific rotation value (ref 4c). See the Supporting Information for details.
(11) Other metals possessing π-coordinating ability were also investigated at low temperature. No marked improvement of the enantioselectivity was observed, although a predictable temperature effect was detected. These results indicate that not only metal species but also suitable Lewis acidity of metal additive are important for the cooperative effect. The experimental details are included in the Supporting Information.
(12) A prolinol ether−transition metal−Brønsted acid cooperative catalysis has been reported; see: Gómez-Bengoa, E.; García, J. M.; Jiménez, S.; Lapuerta, I.; Mielgo, A.; Odriozola, J. M.; Otazo, I.; Razkin, J.; Urruzuno, I.; Vera, S.; Oiarbide, M.; Palomo, C. Asymmetric synthesis of propargylic alcoholsviaaldol reaction of aldehydes with ynals promoted by prolinol ether−transition metal−Brønsted acid cooperative catalysis. *Chem. Sci.* **2013**, *4*, 3198−3204.
(13) The allylation reaction of *p*-tolualdehyde was conducted in the presence of (*R*)-**5** with CuBr as well as without CuBr to give almost the same enantioselectivity. This result indicates that CuBr does not affect the enantioselectivity of the allylation reaction using *p*-tolualdehyde which does not possess an alkyne moiety. Consequently, it is considered that CuBr does not coordinate to the oxygen atom of chiral phosphoric acid, boron reagent, or aldehydes. See the Supporting Information for experimental details and discussion about the role of CuBr.
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