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Catalytic Enantioselective Allenylation Reactions of Aldehydes with Tethered Bis(8-quinolinolato) (TBOx) Chromium Complex

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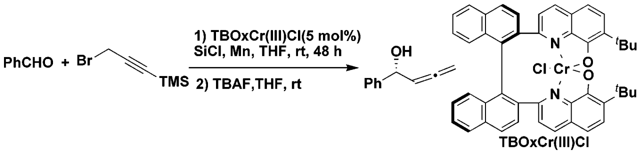
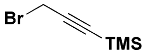
Allenes have proven to be versatile and useful intermediates in organic synthesis due to the existence of the two orthogonal π-bonds.[1] Recently, α-allenic alcohols have drawn much attention because of their unique reactivities and the ease of further conversion into compounds with other functional groups.[1,2] Practical methods for the synthesis of α-allenic alcohols by coupling propargylic reagents with carbonyl groups have often been limited by lack of chemoselectivity as well as enantioselectivity. This is due to the ambient nature of propargylic carbanions, which generally exist as an equilibrium mixture of allenic and propargylic organometallic derivatives.[1a,d,3] Despite these complications, several methods have been developed for the regiospecific construction of α-allenic alcohols in recent years.[1d,4] Among these enantioselective synthetic methods,[1f,5] only a very limited number of catalytic asymmetric allenylation have been reported.[6,7] The nucleophilic addition of organochromium reagents to aldehydes is a powerful C−C bond-forming method.[8] The allenylation reactions between aldehydes and propargylic halides catalyzed by chromium complexes are known to be very useful due to excellent chemoselectivity, broad compatibility with different functional groups, and environmentally benign process.[7] However, there are still some difficulties in terms of (1) the enantioselectivities of α-allenic alcohols, (2) scope of substrates, and (3) the ease of operation with commercially available reagents.

We earlier developed and synthesized a tethered bis(8-quinolinolato) (TBOx) chromium catalyst and applied it to asymmetric pinacol coupling reactions[9] of aldehydes and asymmetric Nozaki−Hiyama allylation reactions.[10] This successful catalytic redox system was further applied to the asymmetric allenylation reaction between benzaldehyde and commercially available 1-trimethylsilyl-3-bromopropyne.

First, TBOxCr(III)Cl (5 mol %) and Mn powder were mixed in THF under an atmosphere of Ar at room temperature. After 10 min, to the reaction mixture was added 1-trimethylsilyl-3-bromopropyne,[11] and the mixture was stirred for 30 min. Then, benzaldehyde and the silyl chloride were added successively and slowly. After 48 h, the isolated crude product was treated with TBAF in THF at room temperature to afford 1-phenylbuta-2,3-dien-1-ol as the only product. If the crude product was treated with 0.5 N HCl in THF, TMS-substituted α-allenic alcohol could be obtained in lower yield.[12] As shown in Table 1, by using TMSCl (1 equiv), the α-allenic alcohol was obtained in 77% yield with only 17% ee (entry 1). When TESCl (1 equiv) was used, the enantioselectivity of the product was increased dramatically accompanied by good yield (entry 4). The different reaction rates between TMSCl (entry 2) and TESCl (entry 5) were observed when no catalyst was applied. If more than 1 equiv of silyl chloride was used, the desired product was generated in higher yield but lower ee (entries 3 and 6). Finally, when 1-trimethylsilyl-3-bromopropyne (1.5 equiv) and TESCl (1 equiv) were applied, the desired α-allenic alcohol was produced with 91% yield and 96% ee (entry 8).

Table 1. Asymmetric Allenylation Reactions of Benzaldehyde



entry		SiCl	yield^a (%)	ee^b (%) (config)^c
1	1 equiv	1 equiv of TMSCl	77	17 (*R*)
2^d	1 equiv	1 equiv TMSCl	37	
3	1 equiv	1.2 equiv of TMSCl	83	8 (*R*)
4	1 equiv	1 equiv of TESCl	71	96 (*R*)
5^d	1 equiv	1 equiv of TESCl	<5	
6	1 equiv	1.2 equiv of TESCl	74	95 (*R*)
7	1.25 equiv	1 equiv of TESCl	82	96 (*R*)
8	1.5 equiv	1 equiv of TESCl	91	96 (*R*)
9^e	1 equiv	1 equiv of TESCl	89	96 (*R*)

[a] Isolated yield after chromatographic purification. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Assigned by comparison of the sign of optical rotation with reported value. [d] No TBOxCr(III)Cl was used. [e] The reaction was complete in 30 h by using TBOxCr(III)Cl (10 mol %).

Under the optimized reaction conditions, a very wide scope of aldehydes was successfully allenylated in moderate to high yields with excellent enantioselectivities. As shown in Table 2, *para*-substituted aromatic aldehydes with either electron-donating or electron-withdrawing groups gave excellent enantioselectivities (entries 1, 4, 5, and 7). However, a higher catalyst loading, more TESCl, and 1-trimethylsilyl-3-bromopropyne had to be applied to achieve higher yields for the benzaldehydes with an electron-withdrawing group (entries 6 and 8). The *ortho*- and *meta*-substituted benzaldehyde could also be allenylated in good yields with good ee (entries 2 and 3). Bulky aryl aldehydes (entries 9 and 10), heterocyclic aldehyde (entry 11), α,β-unsaturated aldehyde (entry12), and aliphatic aldehydes (entries 13−15) proved to be good substrates for this method.

To further explore the substrate scope, the allenylation reactions of aldehydes with terminally alkyl-substituted propargylic bromide, which had never succeeded with high enantioselectivities by Cr-catalyzed asymmetric allenylation reactions previously,[13] were examined under the optimized reaction conditions. As shown in Table 3, the allenylation reaction between benzaldehyde and commercially available 1-bromo-2-butyne provided 2-methyl-1-phenylbuta-2,3-dien-1-ol in 84% yield with 97% ee as the major product with <5% yield of homopropargylic alcohol (entry 1). In the allenylation of other aromatic aldehydes with an electron-donating or electron-withdrawing group (entries 2 and 3), an aliphatic aldehyde (entry 4) also gave excellent enantioselectivities with moderate to good yields when R_2 was the methyl group. Increasing the size of the R_2 group caused the enantioselectivities of the allenylation reactions to go down slightly. When R_2 is an ethyl group, benzaldehyde and hydrocinnamylaldehyde were allenylated in good yield with excellent ee (entry 5 compared to entry 1, and entry 6 compared to entry 4). When R_2 is a phenyl group, benzaldehyde was allenylated in 58% yield with 88% ee (entry 7 compared to entries 1 and 5).

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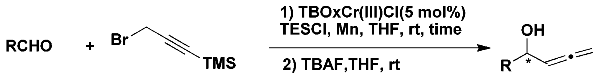
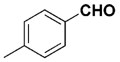
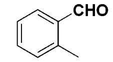
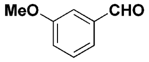
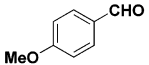
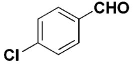
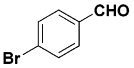
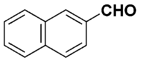
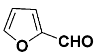
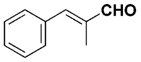
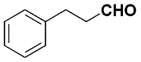
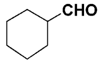
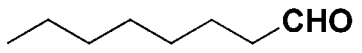
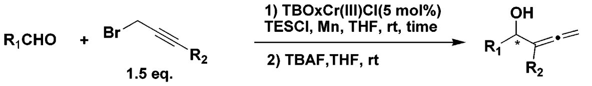
Table 2. Asymmetric Allenylation Reactions of Aldehydes

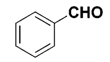
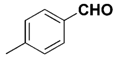
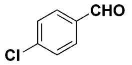
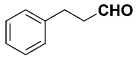
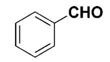
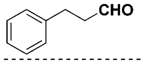
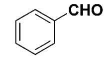


entry	RCHO	time (h)	yield^a (%)	ee^b (%)
1		48	83	90
2		60	77	84
3		48	85	96
4		48	81	95
5		60	35	94
6[c]		60	51	91
7		60	40	93
8[c]		60	57	92
9		60	33	93
10[c]		60	45	90
11		48	79	97
12		60	51	90
13		48	81	93[d]
14		60	72	90[d]
15		60	75	85[d]

[a] Isolated yield after chromatographic purification. [b] Enantiomeric excess was determined by chiral HPLC or GC analysis. [c] 1-Trimethylsilyl-3-bromopropyne (2 equiv), TESCl (1.2 equiv), and TBOxCr(III)Cl (7 mol %) were used. [d] The absolute configuration of the product was determined to be *S*.

Table 3. Asymmetric Allenylation Reactions of Aldehydes with Terminally Alkyl-Substituted Propargylic Bromide



entry	R_1CHO	R_2	time (h)	yield^a (%)	ee^b (%)
1		Me	48	84	97
2		Me	48	76	97
3		Me	60	48	90
4		Me	48	69	93[c]
5		Et	60	87	95
6		Et	60	72	92[c]
7		Ph	60	58	88

[a] Isolated yield after chromatographic purification. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] The absolute configuration of the product was determined to be *S*.

In summary, TBOxCr(III)Cl was shown to efficiently catalyze the asymmetric allenylation reactions of both aromatic and aliphatic aldehydes. Utilizing this methodology, most of the difficulties were overcome: (1) Excellent enantioselectivities (up to 97% ee) for the allenylation reaction of versatile aldehydes were obtained. (2) Easy operation with commercially available terminally substituted propargylic bromide could be achieved. (3) First success for the allenylation reactions of aldehydes with terminally alkyl-substituted propargylic bromides that provided excellent chemoselectivities (α-allenic alcohol as the major product in up to 84% yield) as well as unprecedented enantioselectivities (up to 97% ee). Studies are currently underway to elucidate the mechanism.[14] The applications of TBOxH in other asymmetric catalysis will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) Some examples: (a) Olsson, L. I.; Claesson, A. *Synthesis* **1979**, *9*, 743−745. (b) Nikam, S. S.; Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 745−747. (c) Friesen, R. W. *Tetrahedron. Lett.* **1990**, *31*, 4249−4252. (d) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180−7184. (e) Laurens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526−8535. (f) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943−7944. (g) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537−2538. (h) Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **2001**, *123*, 5578−5579. (i) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759−1774. (j) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem.−Eur. J.* **2002**, *8*, 1719−1729. (k) Xu, D.; Xu, Y.; Li, L.; Ma, S. *Chem.−Eur. J.* **2002**, *8*, 5012−5018. (l) Yoneda, E.; Zhang, S.; Zhou, D.; Onitsuka, K.; Takahashi, S. *J. Org. Chem.* **2003**, *68*, 8571−8576. (m) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376−1385. (n) Hashima, S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387−1389.
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(7) For a recent excellent report about Cr-catalyzed asymmetric allenylation reactions of aldehydes, see: Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252−255.
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(11) The silyl group of the propargylic bromide affected the yields and enantioselectivities. See Scheme 1 in Supporting Information.
(12) See Scheme 2 in Supporting Information.
(13) For example, ref 7 in comparison to entry 1 in Table 3.
(14) See Scheme 3 in Supporting Information for the proposed catalytic cycle and transition structures.

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