Highlight Review

Asymmetric Catalytic Redox System: Tethered Bis(8-quinolinolato) (TBOx) Chromium(III/II) Complexes

Hisashi Yamamoto* and Guoyao Xia

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Abstract

The TBOxCr^{III}Cl/TBOxCr^{II} system is ideal for catalytic asymmetric redox process. Because of the electron density of the TBOxH ligand high turnover numbers are expected, hence allowing decrease in the chromium catalyst loadings and acceleration of the reaction rate. High reactivity and high diastereo-/enantioselectivity are shown in asymmetric pinacol coupling reactions of aldehydes, asymmetric NH allylation reaction of aldehydes, asymmetric allenylation reactions of aldehydes, and some other reactions. These proceed exceedingly efficiently catalyzed by the TBOxCr^{III}Cl redox system due to the well-designed chiral environment of the ligands and the cis-β configuration of the center Cr metal.

♦ Introduction

A redox system is important for the reactions using poisonous metals since the amount of harmful metal required can be significantly reduced.[1] For example, the Cr^{II}-mediated C–C bond-forming reaction originally developed by Nozaki and Hiyama has been studied extensively because of its utility in complex natural product synthesis due to its high chemoselectivity and excellent compatibility with various functional groups.[2] Although a huge excess of toxic chromium salts had been required to complete the reaction in the early stage, the catalytic redox system reduced the quantity of these salts, making these reactions more valuable and environmentally benign. Furthermore, enantioselective reactions based on chiral catalysts rather than on stoichiometric chiral reagents or substrate-bound chiral auxiliaries can be advantageous.

Organometallic reagents prepared by the Barbier protocol[3] have found numerous applications in organic synthesis. In general, the organometallic reagent is prepared in situ by an oxidative addition reaction between a reactive organohalide and more than a stoichiometric amount of the redox active metal (Figure 1).[4]

A catalytic redox process can be designed employing a couple of metals, one of them being the stoichiometric reductant (Figure 2). However, only a small number of catalytic redox processes based on titanium, chromium, samarium, and vanadium have been described.[5] These systems are based on two concepts, namely the use of a reductant which is usually a metal or low-valent metal complex, capable of restoring the catalytic active species, and the use of a "scavenger" able to liberate the organic product by cleaving a stable metal–oxygen bond. Apparently, the future goal of a general catalytic redox process is the use of electrons alone.

Figure 1. Preparation of organometallic reagent.

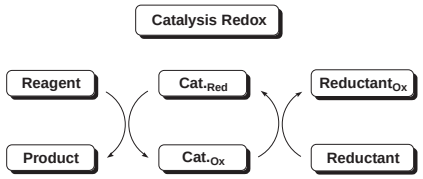
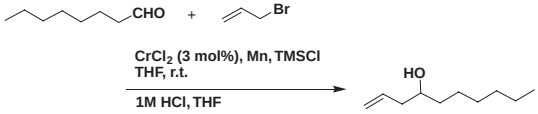


Figure 2. Catalytic redox process.

♦ Catalytic Cr^{III}/Cr^{II} Redox System

The addition of an organochromium nucleophile to a carbonyl compound leads to the formation of a chromium alkoxide as the primary product. The high stability of the resulting O–Cr^{III} bond serves as the thermodynamic sink that drives the conversion and can be used to compensate for considerable strain energy build up in the organic product. Stoichiometric Nozaki–Hiyama reactions required 2 mol of Cr^{II} per 1 mol of organic halide for the formation of the nucleophile; in practice, Cr^{II} was generally used in huge excess.[2] A catalytic version of the NH reaction was desirable.

Recent investigations by Fürstner have addressed this issue.[6] The remarkable key feature of their modification consists of the silylation of the chromium alkoxide species initially formed by means of R_3SiCl, to release the metal salt from the organic product. The liberated Cr^{III}, which is much less toxic than chromium(VI),[7] can then be re-reduced in situ to the active species by means of a stoichiometric and nontoxic reducing agent. Cheap, commercial Mn powder serves this purpose very well because it forms an efficient redox couple with Cr^{III}[8] but does not react or reacts very slowly on its own with organic compounds.[9] Further, the accumulating Mn^{II} salts are essentially nontoxic and exhibit rather weak Lewis acidity. The basic catalytic cycle for NH reactions employing CrX_n ($n = 2$ or 3), Mn, and a chloro-



Scheme 1. Catalytic NH reactions.

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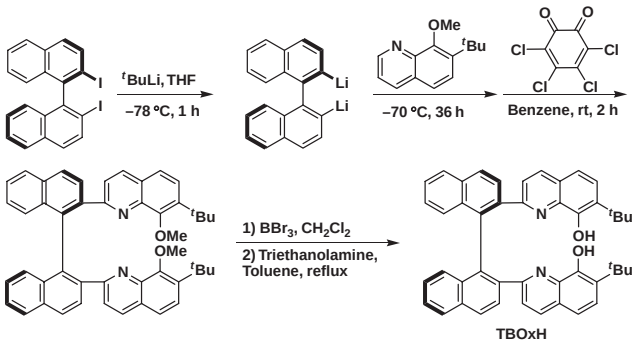


Scheme 2. Synthesis of chiral TBOxH.

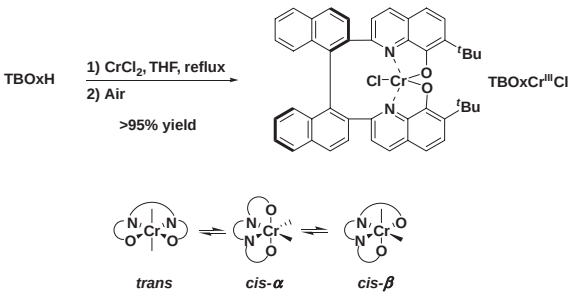
silane as the mediator is exemplified in Scheme 1. It should be emphasized that this overall process does not imply that each individual step exactly follows the displayed order and rationale. This catalytic setup turn out to be applicable to all types of Cr^{II}-mediated reactions without compromising the yield, the chemo- and diastereoselectivity, or the compatibility with various functional groups.[10]

♦ *TBOxCr^{III}Cl*

The development from an achiral template into an asymmetric chiral ligand, which is called TBOxH, was successfully achieved in several steps from 2,2′-diiodo-1,1′-binaphthyl and 7-*tert*-butyl-8-methoxyquinoline (Scheme 2) with an overall 90% yield.[11]

With the TBOxH ligands in hand, the coordination ability of this type of new ligand was tested. As originally designed, with N_2O_2 type of coordination pattern, TBOxH ligand showed very good coordination abilities and formed different kinds of TBOxM complexes (tetrahedral or octahedral configurations) with different metals. TBOxCr^{III}Cl complex was synthesized from $CrCl_2$ with over 95% yield (Scheme 3). TBOxH and $CrCl_2$, as $CrCl_2$ has better coordination ability with N_2O_2-type ligands, were mixed under anhydrous nitrogen, and then refluxed in THF for overnight followed by oxidation in the air for 1 day. The desired TBOxCr^{III}Cl could be obtained as dark brown solid, which is a very stable complex even after being exposed to the air on a benchtop for weeks.

TBOxCr^{III}Cl may have a total of three geometric isomers as shown in Scheme 3, given that it adapts octahedral coordination. The X-ray structure of *rac*-TBOxCrCl, which has a very unique structure of a 9-member ring as well as two 5-member rings, revealed that TBOxH ligand is bound to the chromium center in a cis-β configuration (Figure 3). A crystal structure of



Scheme 3. Synthesis of chiral TBOxCr^{III}Cl.

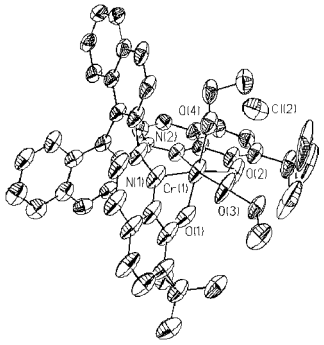


Figure 3. X-ray crystal structure of [TBOx(EtOH)$_2$Cr^{III}]Cl.

TBOxCr^{III}Cl from EtOH provided valuable information to support our designs for the cis-β configuration.

From the crystal structure of TBOx(EtOH)$_2$Cr^{III}Cl, we can easily tell that two EtOH molecules coordinate to the center Cr at cis positions to each other. They fit into the concave site and are ready to exchange with other substrates or reagents. The binaphthyl backbones fix the two naphthalene rings and two quinoline rings, which provide a very tight enantio-environment around the center Cr metal. The two reactive sites are very close to each other and only two faces around the concave site are open. Although the free TBOxH ligand has C_2-symmetry, the produced cis-β metal complex does not. Thus, the metal center of the resulting cis-β complex is chiral and two of the coordination sites (in case of a hexacoordinate complex) are non-equivalent. Furthermore, because of the C_2-symmetry configuration of chiral ligand, we do not need to worry about the possible generation of two stereoisomers. The TBOxH ligands thus provide us great opportunity for a new asymmetric synthesis. In fact, a suitably substituted cis-β ligand is able to provide a nice concave-type reaction site that should enable distinct chiral recognition. Our TBOxH ligands are completely free from any equilibrium problem since the cis-β configuration is the only possible configuration of TBOxH ligands. These unique features of this TBOxCr^{III}Cl complex with cis-β configuration are expected to guarantee high reactivity among the reagents, which could fit into the concave site, and high enantioselectivities.

TBOxCr^{III}Cl could be easily reduced by a reducing reagent, such as a simple metal (Mn, Zn, Al, etc.), to chiral TBOxCr^{II} complex. This special redox system has proven to be very efficient and powerful and has been applied to several different asymmetric catalyses.

♦ *Asymmetric Pinacol Coupling*

The reductive dimerization of carbonyl compounds, especially aldehydes and ketones, to give diols is an important method for constructing vicinally functionalized carbon–carbon bonds.[12] To synthesize such complicated compounds, the efficient control of the stereochemistry in the pinacol coupling reactions is of great importance. Another significant part of the pinacol coupling reaction includes the construction of a catalytic system of low-valent metals.

Simple chromium(II) salts such as $CrCl_2$ and $Cr(ClO_4)_2$ have been reported to promote radical-mediated pinacolic coupling reaction either as a stoichiometric reagent or as a catalyst in the presence of a stoichiometric co-reductant. However, the identification of a catalytic asymmetric pinacol coupling reac-

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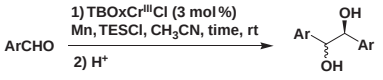
Table 1. Asymmetric Pinacol coupling of aromatic aldehydes



ArCHO	Time/h	Yield/%	dl:meso	dl/%ee
C_6H_5	10	94	52:1	97
o-$CH_3C_6H_4$	18	93	65:1	98
p-ClC_6H_4	9	94	36:1	98
p-BrC_6H_4	10	91	29:1	98
p-$CH_3C_6H_4$	12	93	37:1	97
1-Naph	14	92	24:1	98
2-Naph	14	88	35:1	95
m-$MeOC_6H_4$	12	92	46:1	97
p-$CF_3C_6H_4$	20	89	11:1	95

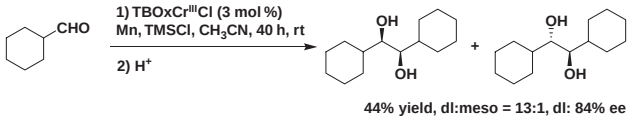
tion has remained a challenge for organic chemistry since not only enantioselectivity but also diastereoselectivity (dl vs. meso) needs to be controlled in a single bond-forming event. High stereoselectivity in pinacol coupling reaction has remained elusive even through stoichiometric protocols.[13] To date, efforts towards this goal have focused on the use of chiral low-valent titanium catalysts.[14]

Fürstner found that the reducing ability of Cp_2Cr towards aromatic aldehydes exceeded that of $CrCl_2$ during the course of his study on chromium-catalyzed NH reaction.[6] The observed difference between the two was attributed to a Cp ligand which is more electron-rich than a chloride ligand. An electron-rich Cr^{II} complex would, therefore, be an attractive candidate as a catalyst for the pinacol coupling reaction. Given the low flexibility for structural modification of chiral Cp-based ligands, our attention was eventually turned to our TBOxH ligand as an electron-rich metal template.

The precatalyst (TBOxCr^{III}Cl), co-reducing agent (Mn), the product scavenger (TESCl), and aldehyde were mixed in CH_3CN under an atmosphere of Ar at room temperature. Significantly, the reaction is effectively catalyzed with 3 mol % of the catalyst, which represents the lowest catalyst/substrate ratio for an asymmetric catalytic pinacol coupling reaction. The isolated crude silyl ethers were treated with aqueous HCl in THF to afford diols in high yields and excellent enantio- and diastereoselectivities. (Table 1).[11]

The synthesis of pinacols from aliphatic aldehydes requires the use of a more efficient redox system than does the corresponding reductive coupling of aromatic systems. To our surprise, the scope of our method was found not to be limited to aromatic aldehyde derivatives, as cyclohexanecarboxaldehyde underwent pinacolization (44% yield, dl:meso = 93:7, 84% ee). This represents the first example of the asymmetric catalysis of an aliphatic pinacol coupling reaction (Scheme 4).[11]

TBOxCr^{III}Cl was shown to efficiently catalyze the asymmetric pinacol coupling reactions of both aromatic and aliphatic aldehydes. This methodology provides an efficient access to



Scheme 4. Asymmetric Pinacol coupling of aliphatic aldehydes.

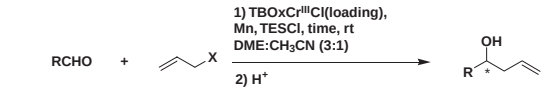
chiral 1,2-diols with excellent enantioselectivities and diastereoselectivities.

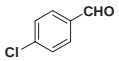
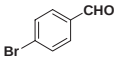
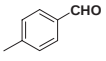
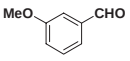
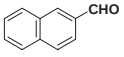
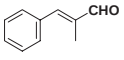
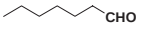
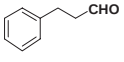
♦ *Asymmetric NH Allylation*

The NH reaction[2,10,15] has proven to be a powerful C–C bond-formation method by virtue of its high chemo- and stereoselectivity and ease of the reaction under mild conditions.[6a,10,16] Catalytic asymmetric NH methodologies have been recognized as important and effective methods and environmentally friendly processes for the synthesis of chiral homoallylic alcohols.

Asymmetric catalysis of NH reactions would allow control over the enantioselectivity, thereby further enhancing the versatility of these powerful transformations. Although there have been a limited number of reports on asymmetric catalysis of these reactions,[17] the enantioselectivities, yields, and the scope

Table 2. Asymmetric NH allylation catalyzed by TBOxCr^{III}Cl



RCHO	X	Loading/mol %	Time/h	Yield/%	ee/%(config.)
	Br	0.5	48	75	86 (R)
	Br	1	24	91	96 (R)
	Br	3	18	93	98 (R)
	Br	10	8	95	99 (R)
	Br	3	18	93	95 (R)
	Br	3	18	93	95 (R)
	Br	3	24	91	96 (R)
	Br	3	24	83	93 (R)
	Br	3	24	81	97 (R)
	Br	3	24	81	93 (R)
	Br	3	24	88	95 (R)
	Br	3	18	86	97 (R)
	Br	3	18	87	95 (R)
	Br	3	18	89	96 (R)
	Br	1	40	79	96 (R)
	Br	3	40	90	98 (R)
	Cl	3	40	68	98 (R)
	Br	10	24	88	98 (R)
	Br	3	40	89	97 (S)
	Cl	3	40	76	98 (S)
	Br	3	18	81	97 (S)
	Cl	3	24	79	97 (S)
	Br	3	24	81	94 (R)
	Cl	3	40	77	95 (R)
	Br	3	40	68	97 (R)
	Cl	3	60	54	98 (R)

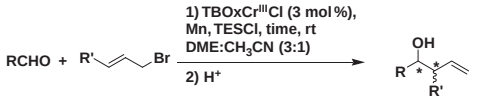
of the substrates were not satisfactory. To overcome these difficulties our TBOxCr^{III}Cl redox system was applied to catalytic asymmetric NH allylation reactions.[18]

After carefully optimizing the experimental parameters, an easy reaction procedure was established for the NH allylation reaction of different aldehydes to afford homoallylic alcohols in good yields and good enantioselectivities (Table 2). The chromium catalyst loading could be decreased to 1 mol % while maintaining good yields and enantioselectivities. Even when 0.5 mol % catalyst was used for the reaction between benzaldehyde and allyl bromide, the desired product in good yield with good ee was afforded. Because aliphatic aldehydes are not as reactive as aromatic aldehydes, the pinacol coupling reactions of aliphatic aldehydes are slower. Due to this, not only allyl bromide but also allyl chloride could be applied to the NH allylation reaction of different aliphatic aldehydes to afford homoallylic alcohols in good yields and good enantioselectivities, albeit with longer reaction time.[18]

As shown in Table 2, the catalyst loading could be decreased to 1 mol % while maintaining good yields and enantioselectivities. Even when 0.5 mol % catalyst was used for the reaction between benzaldehyde and allyl bromide, (*R*)-1-phenylbut-3-en-1-ol in 75% yield with 86% ee was afforded. By using 10 mol % catalyst, 99% ee for benzaldehyde and 98% ee for cyclohexanecarboxaldehyde with good yields were obtained. Because aliphatic aldehydes are not as reactive as aromatic aldehydes, the pinacol coupling reactions of aliphatic aldehydes are slower. Due to this, not only allyl bromide but also allyl chloride could be applied to the NH allylation reaction of different aliphatic aldehydes to afford homoallylic alcohols in good yields and good enantioselectivities, albeit with longer reaction time. The present catalyst system proved to be quite tolerable to changes in steric effect and in electron density effect. We achieved good yields and over 95% ee with other aryl aldehydes as well. Additionally, an α,β-unsaturated aldehyde also proved to be a good substrate.

To further explore the substrate scope, more allylic bromides were used in the NH allylation of aldehydes. As shown in Table 3, surprisingly, the observed diastereoselectivity of the crotylation of benzaldehyde was high with a 4.4:1 ratio favoring anti-product in 84% yield with 97% ee for both anti and syn forms. The crotylation of cyclohexanecarboxaldehyde gave the homoallylic alcohols with a 6.3:1 ratio of anti to syn in 73% yield with 96% ee (anti form) and 97% ee (syn form). When the size of R was decreased, lower diastereoselectivities were observed with higher yield and similar enantioselectivities.

Table 3. Addition of other allyl bromides to aldehydes



RCHO	R'	Time/h	Yield/%	anti:syn	ee(%)anti/syn
CHO	CH_3	36	76	5.5:1	95/96
	n-C_3H_7	48	71	8.4:1	91/91
	n-C_5H_{11}	60	65	10.3:1	90/87
CHO	CH_3	60	73	6.3:1	96/97
CHO	CH_3	36	88	4.2:1	94/94

More interestingly, when the size of R′ was increased, higher diastereoselectivities were observed with only a slight decrease of yields and enantioselectivities. To the best of our knowledge, the observed diastereoselectivities and the enantiomeric excesses for each diastereomer of those aldehydes are the highest to date in an asymmetric crotylation using a Cr^{II}-based system.

TBOxCr^{III}Cl was shown to efficiently catalyze the asymmetric NH allylation reaction of both aromatic and aliphatic aldehydes. (1) Excellent enantioselectivities (up to 99% ee) for the NH allylation reaction of aldehydes were obtained. (2) A very wide scope of aldehydes was investigated. (3) The lowest catalyst/substrate ratio (0.5 mol %) for an asymmetric catalytic NH allylation reaction was achieved. (4) Crotylation of benzaldehyde led to a 5.5:1 ratio of anti to syn and >95% ee for both diastereomers. A plausible mechanism and transition state of the key step were proposed.

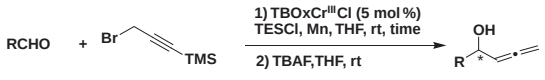
♦ *Asymmetric Allenylation Reactions*

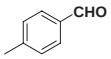
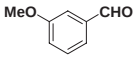
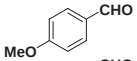
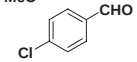
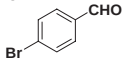
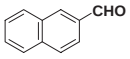
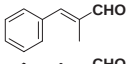
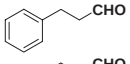
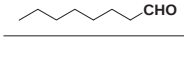
Allenes have proven to be versatile and useful intermediates in organic synthesis due to the existence of the two orthogonal π-bonds.[19] Recently, α-allenic alcohols have drawn much attention because of their unique reactivities and the ease of further conversion into compounds with other functional groups.[20] Practical methods for the synthesis of α-allenic alcohols by coupling propargylic reagents with carbonyl groups have often been limited by lack of regioselectivity as well as enantioselectivity. This is due to the ambient nature of propargylic carbon ions, which generally exist as an equilibrium mixture of allenic and propargylic organometallic derivatives.[21] In spite of these complications, several methods have been developed for the regiospecific construction of α-allenic alcohols in recent years.[22]

Among these enantioselective synthetic methods,[23] a very limited number of catalytic asymmetric allenylations have been reported.[24] Nucleophilic addition of organochromium reagents to aldehydes is a powerful C–C bond-forming method. 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 an environmentally benign process. 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.

The successful catalytic TBOxCr$^{III/II}$ redox system was further applied to the asymmetric allenylation reaction.[25] Under the optimized reaction conditions, a very wide scope of aldehydes were successfully allenylated in moderate to high yields with excellent enantioselectivities (Table 4). Under the optimized reaction conditions, a very wide scope of aldehydes were successfully allenylated in moderate to high yields with excellent enantioselectivities. The aromatic aldehydes with either electron-donating or electron-withdrawing groups gave excellent enantioselectivities. However, a higher catalyst loading, more TESCl and 1-trimethylsilyl-3-bromopropyne had to be applied to achieve higher yields for the benzaldehydes with electron-withdrawing group. Ortho- and meta-substituted benzaldehyde could also be allenylated in good yields with good ee. Bulky aryl aldehydes, heterocyclo aldehyde, α,β-unsaturated aldehyde, and aliphatic aldehydes proved to be good substrates

Table 4. Asymmetric allenylation of aldehydes



RCHO	Time/h	Yield/%	ee/%
	48	91	96
	48	83	90
	60	77	84
	48	85	96
	48	81	95
	60	51	91
	60	57	92
	60	45	90
	48	79	97
	60	51	90
	48	81	93
	60	72	90
	60	75	85

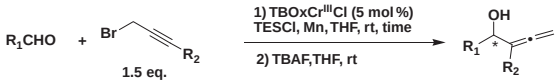
for this method. Although the usual reactions time were about 48 to 60 h, all the products achieved the highest enantioselectivities which had ever achieved by catalytic asymmetric allenylation reactions catalyzed by a $Cr^{III/II}$ redox system.

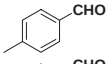
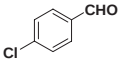
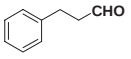
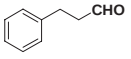
The silyl group of the propargylic bromide was recognized to affect the yields and enantioselectivities as well. If the size of the silyl group increased further, the yields and enantioselectivities of the products went down dramatically. To further explore the substrate scope, the allenylation reactions of aldehydes with terminally alkyl-substituted propargylic bromide, which had never succeeded with high enantioselectivities by Cr-catalyzed asymmetric allenylation reactions previously, were examined under the optimized reaction conditions.

As shown in Table 5, the allenylation reaction between benzaldehyde and commercial available 1-bromo-2-butyne provided 2-methyl-1-phenylbuta-2,3-dien-1-ol in 84% yield with 97% ee as major product and <5% yield homopropargylic alcohol. The allenylation of other aromatic aldehydes with and aliphatic aldehyde 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 decrease slightly.

TBOxCr^{III}Cl was shown to efficiently catalyze the asymmetric allenylation reactions of both aromatic and aliphatic aldehydes. Utilizing this methodology, (1) Excellent enantioselectivities 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 provided excellent regioselectivities as well as enantioselectivities.

Table 5. Allenylation reactions with terminally alkyl-substituted propargylbromide



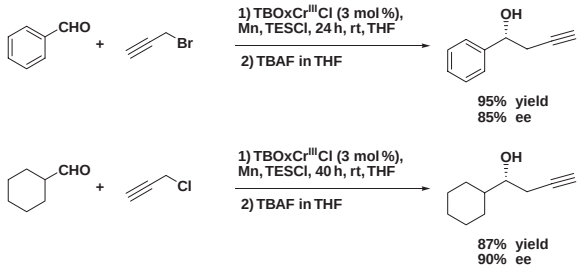
R$_1$CHO	R$_2$	Time/h	Yield/%	ee/%
	Me	48	84	97
	Me	48	76	97
	Me	60	48	90
	Me	48	69	93
	Et	60	87	95
	Et	60	72	92
	Ph	60	58	88

♦ *Other Asymmetric Reactions*

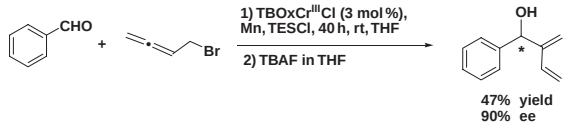
Because our silyl, alkyl, or aryl substitute propargyl bromides produce chiral allenyl alcohols regioselectively by going through propargyl chromium intermediate, we anticipated having a good regioselectivity of propargylation reaction from simple proparyl bromide. The intermediate allenyl chromium species is generated regioselectively under our preliminary experiment conditions for this reaction. Fine tunings of the reaction conditions gave us a nice authentic procedure for this asymmetric transformation. As shown in Scheme 5, both aromatic and aliphatic aldehydes afforded desired homopropargyl alcohols with good yield and moderate enantioselectivites.[26]

Although the asymmetric NH reaction remained unsolved with our TBOxCr^{III}Cl redox system, an alternate method was developed to afford the substituted allylic alcohol in moderate yield and enantioselectivity. As shown in Scheme 6, the reaction between benzaldehyde and allenylic bromide afforded 2-methylene-1-phenylbut-3-en-1-ol in 47% yield with 90% ee.[26]

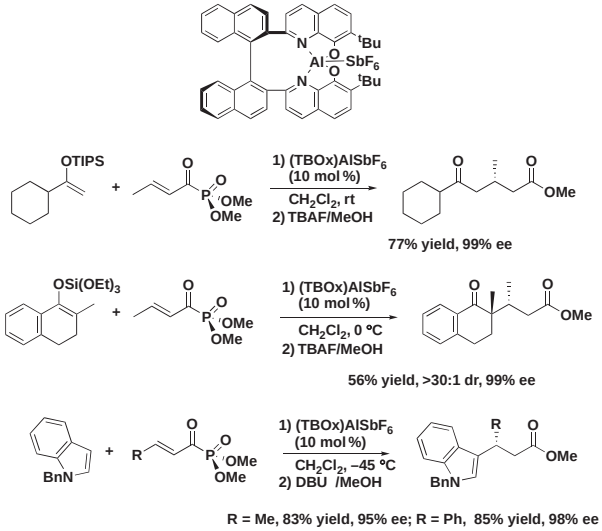
As described earlier, a TBOx ligand can have excellent features not only for chromium-based redox systems but also for various other asymmetric syntheses using more Lewis acidic metal ions. For example, it was found that a new chiral tethered



Scheme 5. Propargylation reactions of aldehyde with TBOxCr^{III}Cl.



Scheme 6. Reaction between benzaldehyde and allenylic bromide.



Scheme 7. Mukaiyama Michael reaction using Al–TBOx catalyst.

bis(8-quinolinolato) (TBOx) aluminum (III) complex effectively catalyzed the highly enantioselective Mukaiyama Michael reaction of silyl enol ethers, including tetrasubstituted enolates that provided access to enantiomerically enriched all-carbon quaternary centers, one of the most difficult problems for asymmetric synthesis (Scheme 7).[27]

♦ Conclusion

The TBOxCr^{III}Cl/TBOxCr^{II} redox system was successfully synthesized and proven to be a very efficient and powerful catalytic asymmetric redox system. Because of the well-designed chiral environment of the ligands and the cis-β configuration of the center Cr metal, high reactivity and high diastereo-/enantio-selectivity were observed in asymmetric pinacol coupling reactions of aldehydes, asymmetric NH allylation reaction of aldehydes, and asymmetric allenylation reactions of aldehydes. Other different types of reactions, which could take advantage of the well-designed chiral environment of the ligands and the cis-β configuration of the center Cr metal, were also demonstrated.

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