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学位の種類	博士（理学）
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学位授与の題目	Asymmetric Addition of Organozinc Reagents to Nitrones. Enantiomeric Enhancement by a Racemic Product-like Additive（ニトロンへの有機亜鉛試薬の不斉求核付加反応．生成物類似ラセミ化合物の添加によるエナンチオ選択性の向上）
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Abstract

Chiral amines are synthetically important target compounds, since they are found in natural products, pharmaceuticals, and other bioactive molecules. During the initial investigation on the enantioselective nucleophilic addition of alkynylzinc reagents to nitrones by utilizing a tartaric acid ester as a chiral auxiliary, an unprecedented "enantiomeric enhancement by a racemic product-like additive", was realized. Based on this exciting result, catalytic enantioselective nucleophilic addition of alkynylzinc reagents to nitrones was developed and excellent results were obtained as expected. Furthermore, the enantioselective addition of phenylzinc reagents to acyclic nitrones bearing an alkynyl substituent on the carbon utilizing the tartaric acid ester as a chiral auxiliary was examined and the enantiomeric enhancement was again observed. Finally, the tandem addition/cyclization reaction in the presence of the additive to give the optically active isoxazoline was also investigated.

The development of practical and efficient methods for construction of chiral molecules is an essential part of programs to explore new medicinal and agrochemical agents. Most common asymmetric reactions rely on the use of catalysts, which contain one metal center within a coordination sphere comprised of chiral ligands. For one metal chiral reaction systems, the control of absolute stereochemistry is sometimes not enough. In my present laboratory, a novel strategy was designed as a chiral reaction system, in which two or three metal centers are complexed utilizing a tartaric acid ester as a chiral auxiliary (**Figure 1**).

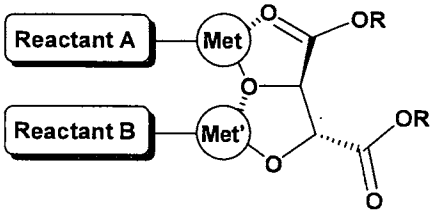
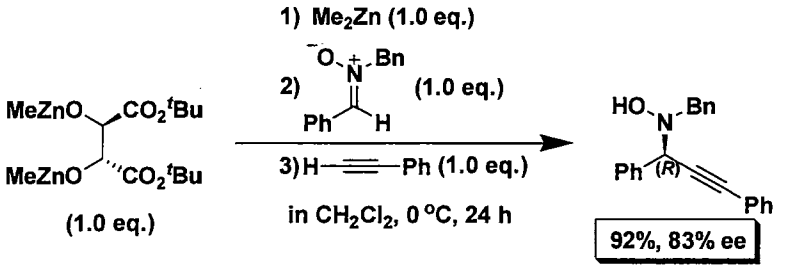


Figure 1 (Met, Met' = Zn, Mg etc.)

Chiral amines are synthetically important target compounds, since they are found in natural products, pharmaceuticals, and other bioactive molecules. For example, chiral benzylic amines are found in biologically active compounds and their building blocks. One of the most attractive approaches to the syntheses of benzylic amines is the enantioselective addition of metal reagents to imine derivatives. Although various methods for the enantioselective synthesis of chiral benzylic amines are known including reduction and alkylation of aromatic imines, direct asymmetric addition reactions to C=N bond is still one of the challenging problems especially in terms of availability of chiral auxiliaries.

My main research is focusing on the development of enantioselective synthesis of chiral benzylic amines by direct asymmetric addition of alkynyl- and phenylzinc reagents to nitrones utilizing tartaric acid ester [(*R*,*R*)-DTBT] as a chiral auxiliary. First, the asymmetric addition of alkynylzincs, which were prepared *in situ* from dialkylzinc and terminal alkynes, to acyclic nitrones was achieved by utilizing (*R*,*R*)-DTBT as a chiral auxiliary to afford the corresponding (*R*)-α-substituted propargylic *N*-hydroxylamines with enantioselectivity of up to 83% ee (**Scheme 1**). However, the enatioselectivity was unsatisfactory. Thus, the asymmetric addition reaction of alkynylzinc to nitrone was reinvestigated and an unprecedented phenomenon, "enantiomeric enhancement by a racemic product-like additive," was found and the remarkable enhancement of enantioselectivities was achieved as described in the following.



Scheme 1

The time course of the reaction was observed in order to confirm how the reaction proceeds. From these results, it was found that the enantioselectivity remarkably increased as the reaction proceeds.

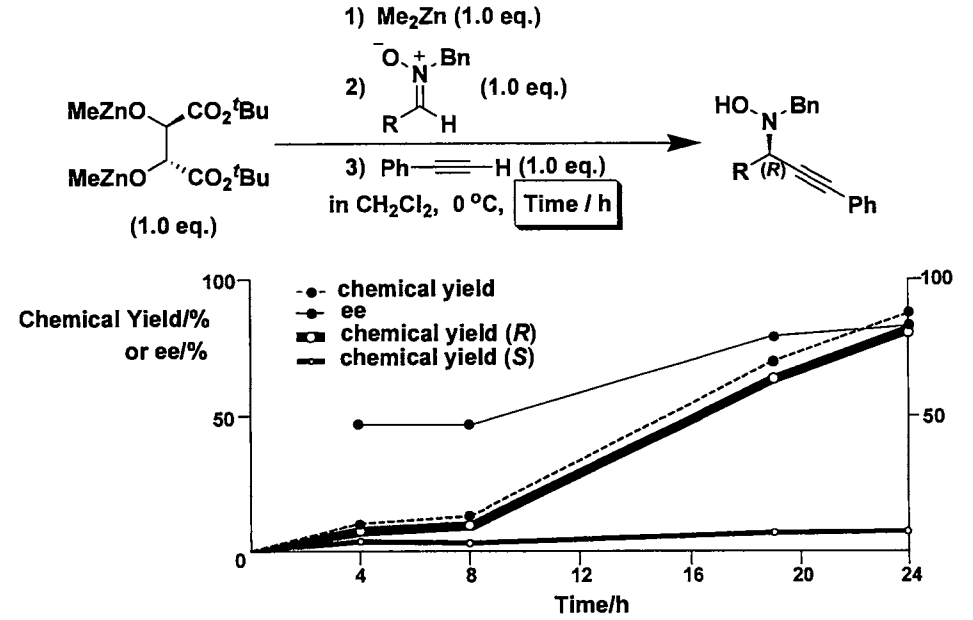
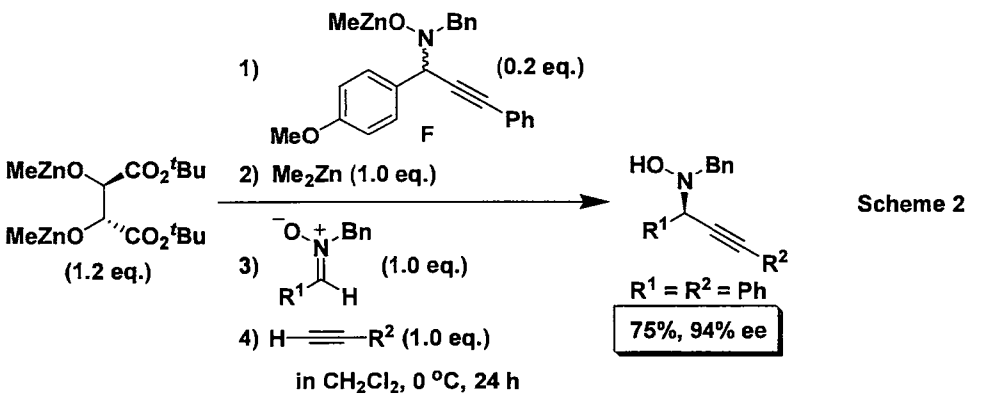


Figure 2. Chemical Yields of (*R*)- and (*S*)-Enantiomers along Reaction Time

Figure 2 shows the relationship between the reaction time and chemical yields of (*R*)- and (*S*)-enantiomers, which are estimated based on the chemical yields and ee. It is noteworthy that after around 8 h, both the chemical yield and ee increased remarkably. Although more precise analysis is necessary, enantioselectivity was relatively low at the initial stage of the reaction. After ca. 8 h, (*S*)-enantiomer was a little accumulated and then (*R*)-enantiomer looked to have been selectively produced. Based on this observation, if the product of the reaction around 8 h was added into the original reaction system, the ee of the product could be enhanced. In order to distinguish the enantiomers of the products at initial and later stages of the reaction from an additive, a product-like substrate was subjected as an additive to the reaction.

Namely, a mixture of 1.2 molar amounts of bis(methylzinc) salt of (*R*,*R*)-DTBT and 1.2 molar amounts of dimethylzinc was treated with 0.2 molar amount of 4-methoxylphenyl-substituted product-like hydroxylamine, followed by addition of 1.0 molar amount of nitrone and phenylacetylene as shown in **Scheme 2**. As expected, the enantiomeric excess was increased to 94% ee.[1]



Scheme 2

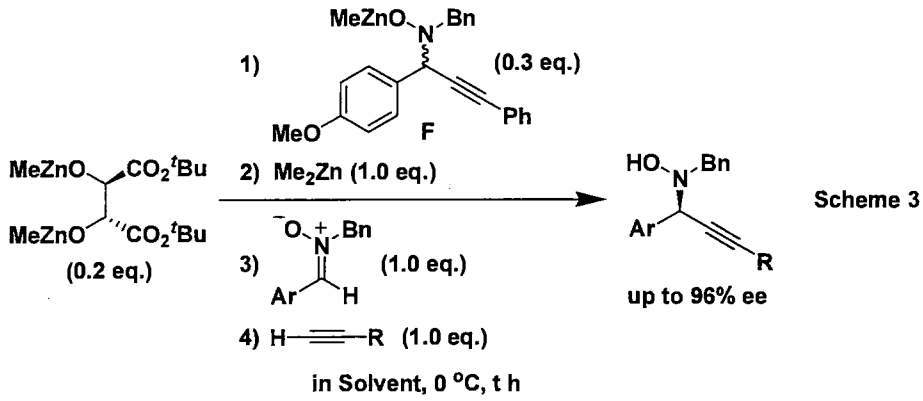
Such a racemic additive was applied to the asymmetric alkynylation of other nitrones with several acetylenes. Compared with the previous results without an additive, the enantioselectivities of the desired products were remarkably improved by employing the racemic product-like hydroxylamine as an additive (**Table 1, Scheme 2**).

Table 1

Entry	R^1	R^2	t / h	Yield / %	ee / %	(Yield / %	ee/ %)[a]
1	Ph	Ph	18	75	94[b]	(89	82)
2	4-$MeOC_6H_4$	Ph	39	80	92[c]	(70	74)
3	4-BrC_6H_4	Ph	18	92	91[c]	(57	77)
4	2-BrC_6H_4	Ph	18	67	95[b]	(71	78)
5	Ph	4-MeC_6H_4	18	70	86[c]	(58	76)
6	Ph	$^nC_6H_{13}$	14	62	79[b]	(48	57)
7	Ph	TMS	20	61	96[b]	(64	77)

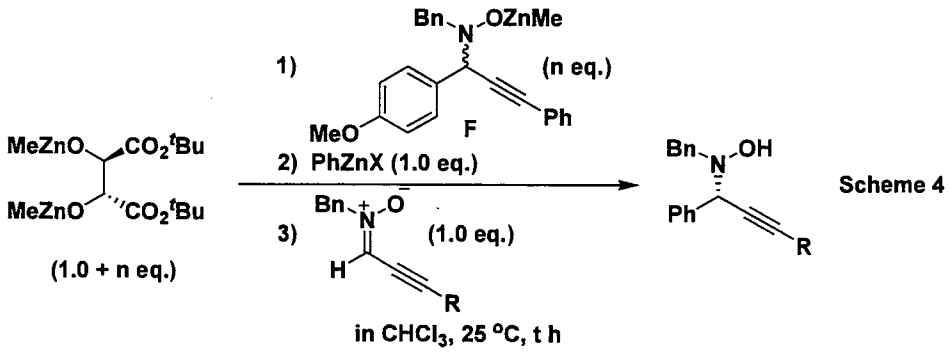
[a]Reactions were carried out without an additive.
[b]Enantiomer's ratio was determined by HPLC analysis (Daicel Chiralcel OJ-H).
[c]Enantiomer's ratio was determined by HPLC analysis (Daicel Chiralcel OD-H).

Based on the fact that a product-like additive enhances the enantioselectivity in the stoichiometric addition reaction, the effect of this product-like additive was also examined in the catalytic reaction system. Namely, to a mixture of 0.2 molar amount of bis(methylzinc) salt of (*R,R*)-DTBT and 0.3 molar amount of methylzinc salt as an additive, which was derived from racemic 4-methoxyphenyl-substituted *N*-propargylic hydroxylamine and dimethylzinc, 1.0 molar amount of dimethylzinc, nitrone and phenylacetylene were subsequently added. The enantioselectivity was also enhanced up to 96% ee by the addition of the racemic product-like additive (**Scheme 3**).[2]



Scheme 3

Furthermore, the enantiomeric enhancement by the addition of a product-like additive was further observed in an enantioselective addition of phenylzinc reagents to acyclic nitrones bearing an alkynyl substituent on the carbon utilizing the tartaric acid ester as a chiral auxiliary to produce *N*-(1-phenyl-3-substituted prop-2-ynyl)hydroxylamines in up to 92% ee (**Scheme 4, Table 2**).[3]



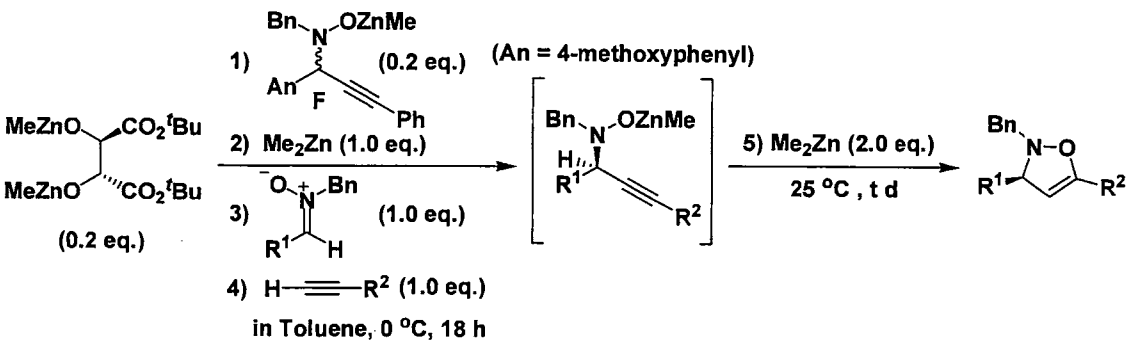
Scheme 4

Table 2

				n = 0.2		n = 0	
Entry	R	X	t / h	Yield / %	ee / %	Yield / %	ee / %
1	Ph	Ph	0.5	72	88[a]	70	64[a]
2		Me[c]	1	75	92[a]		
3	4-$CH_3C_6H_4$	Ph	1	75	87[a]	80	77[a]
4		Me[c]	1	66	87[a]		
5	4-BrC_6H_4	Ph	1	64	90[a]	68	53[a]
6		Me[c]	1	70	90[a]		
7	$^nC_6H_{13}$	Ph	1	67	82[b]	61	52[b]
8		Me[c]	1	67	87[b]		

[a]Enantiomer's ratio was determined by HPLC analysis (Daicel Chiralcel OD-H).
[b]Enantiomer's ratio was determined by HPLC analysis (Daicel Chiralcel OJ-H).
[c]PhZnMe was prepared *in situ* from 0.5 eq. of Ph_2Zn and 0.5 eq. of Me_2Zn.

Previously, it was found that when the addition reaction of alkynylzinc reagent to nitrone was carried out at room temperature, the intermediary addition product cyclized to give the corresponding 4-isoxazoline. Compounds bearing 4-isoxazoline ring skeletons are the key components of optically active nitrogen-containing substances, which have potentially high value in chemical and medicinal fields. Based on the results of the investigation described above, in which the advantage of the effect of the additive was revealed, the tandem addition/cyclization reaction between acetylide and nitrone was examined in the presence of an additive, and the substrate scope was also investigated (**Scheme 5, Table 3**).



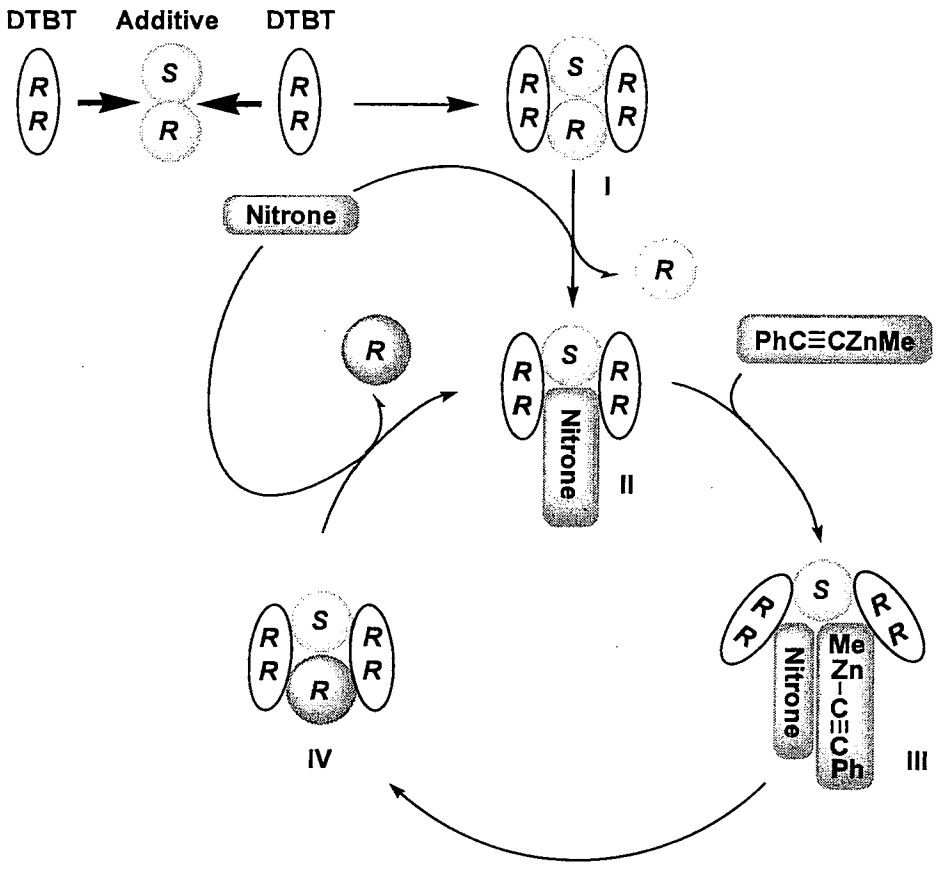
Scheme 5

Table 3

Entry	R^1	R^2	t / d	Yield / %	ee / %
1	Ph	Ph	1	73	91[a]
2	4-BrC_6H_4	Ph	3	72	93[a]
3	2-BrC_6H_4	Ph	2	51	86[b]
4	Ph	4-$PenC_6H_4$	3	42	93[a]
5	Ph	4-BrC_6H_4	3	62	85[a]
6	Ph	$^tBuOCH_2$	1	43	24[a]
7	Ph	$^nC_4H_9$	3	70	80[a]
8	Ph	$^nC_6H_{13}$	3	63	85[a]

[a]Enantioselectivity (% ee) was determined by HPLC analysis (Daicel Chiralcel OD-H).
[b]Enantioselectivity (% ee) was determined by HPLC analysis (Daicel Chiralcel IA).

Although the exact reaction mechanism of the "enantiomeric enhancement by a racemic product-like additive" is unclear, we proposed a possible mechanism below based on various facts observed in the present investigation (**Scheme 6**).



Scheme 6

References

(1) Wei, W.-L.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2006**, *35*, 176.

(2) Konishi, A.; Wei, W.-L.; Kobayashi, M.; Fujinami, S.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2007**, *36*, 44.

(3) Wei, W.-L.; Hamamoto, Y.; Ukaji, Y.; Inomata, K. *Tetrahedron:Asymmetr.* **2008**, *19*, 476.
(4) Wei, W.-L.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Heterocycles in press.*

学位論文審査結果の要旨

本学位論文に対して，各審査委員が参考論文等の関連資料を含めた予備審査を行い，さらに平成21年1月28日の口頭発表における質疑応答（最終試験に代える）の結果を踏まえ，同日開催された審査委員会において以下の通り判定した。

本論文は，当該研究室において開発された酒石酸エステルを不斉源として用いる「複核キラル反応場の創生」という基本的概念に基づいて，鎖状ニトロンへの有機亜鉛試薬の不斉求核付加反応について詳細に検討した結果について報告したものである。すなわち，酒石酸エステルを化学量論量用いたニトロンへの亜鉛アセチリドの不斉求核付加反応について，その経時変化を注意深く観察し，結果的に，生成物に類似した構造を有するラセミ化合物を添加することによって，目的生成物のエナンチオ選択性がいずれも著しく向上するという新奇な現象を見出した。この現象は，化学量論的な反応にとどまらず，触媒的不斉求核付加反応や，アルキニル置換基を有するニトロンへのフェニル亜鉛試薬の付加反応，さらに不斉求核付加反応に引き続く分子内環化反応の系においても同様に有効に作用することを明らかにするなど，不斉合成反応開拓に当たって有用な前例のない興味深い現象を見出した。これらの優れた成果は，博士（理学）の学位を与えるに充分値するものと判定した。