Catalytic Asymmetric Addition of Alkynylzinc Reagents to Nitrones

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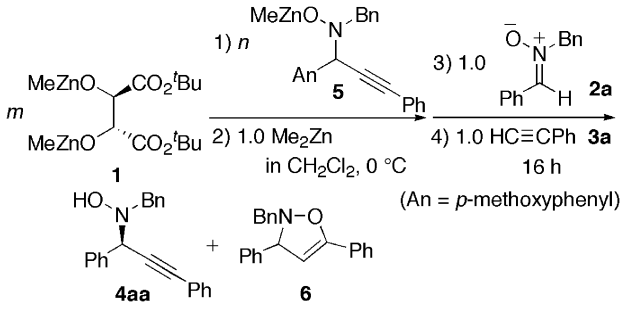
The catalytic asymmetric addition of alkynylzinc reagents, which were prepared in situ from dimethylzinc and 1-alkynes, to nitrones was achieved by utilizing di(*t*-butyl) (*R*,*R*)-tartrate as a chiral auxiliary to afford the corresponding optically active (*R*)-*N*-(α-substituted)propargylic hydroxylamines. By the addition of methylzinc salt of a product-like racemic hydroxylamine, enantioselectivity of the *N*-propargylic hydroxylamines was enhanced up to 96% ee.

The catalytic asymmetric C–C bond formation via nucleophilic addition of a C-nucleophile to imine functions provides one of the most important method for synthesizing optically active amines, which are versatile building blocks for the optically active nitrogen-containing compounds. Especially, the addition of alkynyl nucleophile has a strategic advantage to produce more functionalized nitrogen-containing substances.[1] However, the catalytic methods for the preparation of optically active propargylic amines are still limited.[2] Very recently we have reported a stoichiometric enantioselective nucleophilic addition of alkynylzinc reagent to nitrones by utilizing tartaric acid ester as a chiral auxiliary.[3] Herein, we describe a catalytic enantioselective addition of alkynylzinc reagents to acyclic nitrones utilizing di(*t*-butyl) (*R*,*R*)-tartrate as a chiral auxiliary.

First the catalytic addition reaction of alkynylzinc reagent to *N*-(benzylidene)benzylamine *N*-oxide (**2a**) was examined in CH_2Cl_2 at 0 °C; i.e., in the presence of 0.2 molar amount of bis(methylzinc) salt of di(*t*-butyl) (*R*,*R*)-tartrate [(*R*,*R*)-DTBT] **1**, prepared in situ from 0.2 molar amount of (*R*,*R*)-DTBT and 0.4 molar amount of dimethylzinc, the nitrone **2a** was treated with phenylacetylene (**3a**) and dimethylzinc (Scheme 1).[1b,4] The reaction proceeded smoothly to give the corresponding (*R*)-*N*-propargylic hydroxylamine **4aa** with the enantioselectivity of 68% ee as shown in Table 1 (Entry 1). This result suggested that the zinc salt **1** can work as a catalyst. Previously we found that a product-like additive enhances the enantioselectivity in the stoichiometric addition reaction.[3] Then, the effect of the product-like additive was examined also in the present catalytic



Scheme 1.

Table 1. Catalytic asymmetric addition of an alkynylzinc reagent to a nitrone **2a** in the presence of a product-like additive **5**[a]

Entry	**5**	*m*[b]	*n*[b]	Yield of **4aa** /%	ee of **4aa** /%[c]	Yield of **6** /%
1	*racemic*	0.2	0	87	68	4
2	*racemic*	0.2	0.1	80	72	5
3	*racemic*	0.2	0.2	93	83	3
4	*racemic*	0.2	0.3	90	83	2
5	*R*	0.2	0.3	85	60	3
6	*S*	0.2	0.3	86	73	3
7	*racemic*	0.2	0.4	94	72	1
8	*racemic*	0.1	0	83	45	4
9	*racemic*	0.1	0.1	83	62	2
10	*racemic*	0.1	0.2	83	61	2
11	*racemic*	0.1	0.3	88	51	7
12	*S*	0	0.2	76	21	3

[a]See ref. 5. [b]The italicized *m* and *n* indicate the molar amounts of **1** and **5** as depicted in Scheme 1, respectively. [c]Enantioselectivities were determined by HPLC analysis (Daicel Chiralcel OD-H).

reaction. Namely, to a mixture of 0.2 molar amount of bis(methylzinc) salt of (*R*,*R*)-DTBT **1** and 0.2 molar amount of methylzinc salt **5** derived from racemic *p*-methoxyphenyl-substituted *N*-propargylic hydroxylamine **4ba** and dimethylzinc, 1.0 molar amount of dimethylzinc, nitrone **2a** and phenylacetylene (**3a**) were subsequently added. The enantioselectivity was again enhanced from 68 to 83% ee (Entry 3). Next, the amount of the product-like additive **5** was investigated. As shown in Table 1, the use of 0.2 or 0.3 molar amount of **5** gave almost the same enantioselection (Entries 1–4 and 7). Using 0.3 molar amount of **5**, more reproducible result was realized (Entry 4).

In order to confirm how the reaction proceeds, the time-courses of the reactions corresponding to Entries 1 and 4 in Table 1 were observed. In the catalytic reaction without the additive **5** (Figure 1a), enantioselectivity was lower at the initial stage and it was slightly increased as the reaction proceeded. At later stage of the reaction, a part of the addition product cyclized to give the corresponding 4-isoxazoline **6**.[4a,6] By the

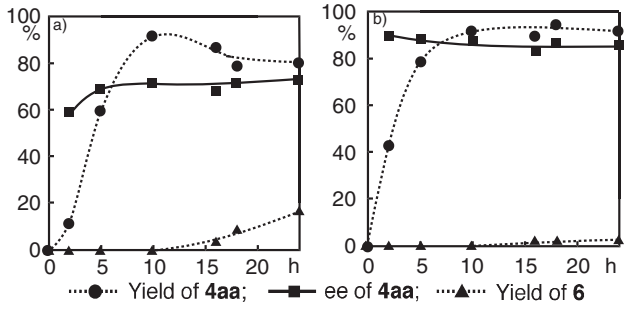
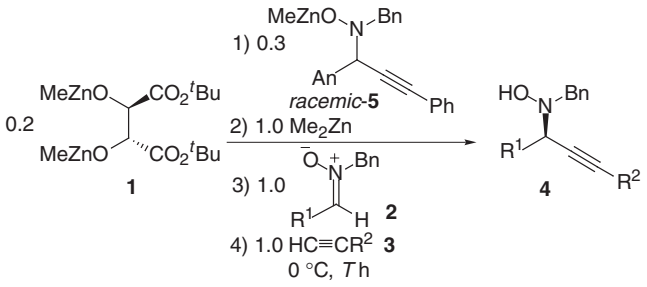


Figure 1. The time-course of the formation of **4aa**. a) Corresponding to Entry 1 in Table 1. b) Corresponding to Entry 4 in Table 1.



Scheme 2.

Table 2. The asymmetric addition of alkynylzinc reagents to nitrones **2** in the presence of a product-like racemic additive[a]

Entry	R^1	**2**	R^2	**3**	Solvent	T/h	**4**	Yield/%	ee/%
1	Ph	**a**	Ph	**a**	CH_2Cl_2	16	**aa**	90	83[b]
2					Et_2O	19		89	83[b]
3					THF	20		62	75[b]
4					toluene	14		92	91[b]
5					xylene	17		80	91[b]
6					EtPh	14		84	95[b]
7					cumeme	17		70	90[b]
8[c]	^{p}MeOC$_6$H$_4$	**b**	Ph	**a**	EtPh	13	**ba**	87	90[b]
9	^{p}BrC$_6$H$_4$	**c**	Ph	**a**	EtPh	18	**ca**	73	90[b]
10	^{o}BrC$_6$H$_4$	**d**	Ph	**a**	EtPh	19	**da**	77	96[d]
11[e]	Ph	**a**	$SiMe_3$	**b**	toluene	7	**ab**	57	88[b]

[a]See ref. 5. [b]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OD-H). [c]A methylzinc salt of *racemic*-**4aa** was used as an additive instead of **5**. [d]Enantioselectivity was determined by HPLC analysis (Daicel Chiralcel OJ-H). [e]The reaction was carried out at rt.

addition of a product-like additive **5** (Figure 1b), induction time was not observed and the enantioselectivity was constantly high from the initial stage. In addition, the cyclization to the 4-isoxazoline **6** was rather retarded.

The influence of the stereochemistry of the additive **5** was investigated. When 0.2 molar amount of methylzinc salt (*R*)- or (*S*)-**5** derived from the corresponding optically pure (*R*)- or (*S*)-**4ba**[7] and dimethylzinc was used as an additive instead of *racemic*-**5**, the enantioselectivity was surprisingly decreased (Entries 5 and 6). Furthermore, it was found that reduction of the amount of methylzinc salt of (*R*,*R*)-DTBT **1** to 0.1 molar amount decreased the catalytic efficiency (Entries 8–11), and poor chiral induction was observed by the use of the only additive **5** without the methylzinc salt of (*R*,*R*)-DTBT **1** (Entry 12). It is noteworthy that this reaction does not proceed in an autocatalytic way, since (*R*)-**4aa** was formed by using (*S*)-**5**.

Next, the addition reactions were carried out in several solvents (Table 2, Entries 1–7). The enantioselectivity was decreased in THF (Entry 3), but remarkably increased in aromatic solvents (Entries 4–7). It was found that ethylbenzene was a choice of solvent to afford **4aa** with excellent enantioselectivity of 95% ee (Entry 6).[8] The several other asymmetric additions of acetylides to nitrones **2** in the presence of *racemic*-**5** were also carried out to furnish the corresponding *N*-propargylic hydroxylamines **4** with excellent enantioselectivities (Entries 8–11).

The absolute configurations of **4aa** and **4ba** were determined to be *R* by chemical correlation[3] and X-ray crystallographic analysis,[7] respectively. The stereochemistries of other products were tentatively assigned to be also *R*.

As described above, a catalytic asymmetric addition of alkynylzinc reagents to acyclic nitrones has been developed. By the addition of a product-like racemic substrate, the asymmetric amplification was observed, and the corresponding *N*-propargylic hydroxylamines were obtained with excellent enantioselectivities.[9]

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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5 The numbers in front of the reagents in Schemes 1 and 2 indicate molar amounts of the reagents used.

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7 The optically pure (*S*)-*N*-propargylic hydroxylamine **4ba**, was obtained as follows: The enantiomerically rich (*S*)-**4ba** (93% ee), obtained by asymmetric addition using a stoichiometric amount of (*S*,*S*)-DTBT,[3] was treated with (*S*)-camphanic chloride and Et_3N in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine in CH_2Cl_2 to give the corresponding ester (74%). Recrystallization from toluene/hexane gave the diastereomerically pure ester. The absolute configuration of the ester was determined to be *S*,*S* by X-ray crystallographic analysis of its single crystal. Crystal data of the ester–toluene (1:1): $C_{40}H_{41}NO_5$, FW 615.77, triclinic, P_1, $a = 6.194(1)$ Å, $b = 10.686(2)$ Å, $c = 13.007(2)$ Å, $\alpha = 91.913(4)^\circ$, $\beta = 91.046(5)^\circ$, $\gamma = 99.929(6)^\circ$, $V = 847.4(3)$ Å^3, $Z = 1$. $D_{calcd} = 1.207$ g/cm^3. $R = 0.042$ ($R_w = 0.059$) for 5909 reflections with $I > 3.00\sigma(I)$ and 416 variable parameters. Reduction of the optically pure ester by $LiAlH_4$ gave the optically pure (*S*)-**4ba** (99%). The optically pure (*R*)-**4ba** was obtained in a similar manner.

8 The enhancement of enantioselectivity by a product-like additive **5** was confirmed even when the asymmetric addition was carried out in ethylbenzene: The reaction in ethylbezene without additive **5** under the same conditions of Entry 1 in Table 1 (the reaction was quenched after stirring for 14 h) gave **4aa** in 76% yield with the enantioselectivity of 84% ee.

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