Asymmetric Addition of Alkynylzinc Reagents to Nitrones Utilizing Tartaric Acid Ester as a Chiral Auxiliary

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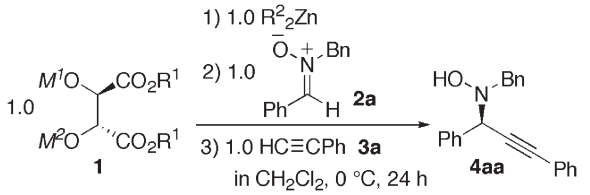
The asymmetric addition of alkynylzinc reagents, prepared in situ from dialkylzinc and 1-alkynes, to nitrones was achieved by utilizing di(*t*-butyl) (*R,R*)-tartrate as a chiral auxiliary to afford the corresponding optically active (*R*)-α-substituted propargylic *N*-hydroxylamines. By the addition of product-like *N*-hydroxylamine, unprecedented enhancement of enantioselectivity was observed to afford the *N*-hydroxylamines up to 95% ee.

The development of efficient methods for C–C bond formation by asymmetric nucleophilic additions to a C=N bond is quite important.[1] The asymmetric addition of acetylides to imines is a useful method for the production of chiral propargylamines, which are versatile building blocks for the optically active nitrogen-containing compounds[2] and can be also encountered as part of biologically active compounds.[3] Although several diastereoselective methods for nucleophilic addition of acetylides had been reported,[2,4] asymmetric addition of acetylides to C=N bond is still regarded as one of the challenging problems especially in terms of availability of chiral auxiliaries.[5] Among the imine compounds, nitrone seems to be a promising candidate because it possesses an electronegative oxygen, which can activate C=N bond and strongly coordinate to metals. We have already reported enantioselective nucleophilic addition of dialkylzinc and Reformatsky-type reagent to nitrones with isoquinoline skeleton by utilizing tartaric acid ester as a chiral auxiliary.[6,7] Herein, we wish to describe an enantioselective addition of alkynylzinc reagents to acyclic nitrones utilizing tartaric acid ester as a chiral auxiliary.[8]

First the 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 1.0 molar amount of biszinc salt of diisopropyl (*R,R*)-tartrate **1A**, derived in situ from 1.0 molar amount of diisopropyl (*R,R*)-tartrate and 2.0 molar amounts of diethylzinc,[9] the nitrone **2a** was treated with phenylacetylene (**3a**) and diethylzinc. After the usual workup, the corresponding (*R*)-propargylic *N*-hydroxylamine **4aa** was obtained with the enantioselectivity of 73% ee as shown in Table 1, Entry 1. As a dialkylzinc for salt formation of tartrate and alkynylzinc reagent, dimethylzinc was slightly more effective than diethylzinc or diisopropylzinc (Entries 1–3). Bulkiness of dialkylzinc, which generated the alkynylzinc, scarcely influenced the enantioselectivity (Entries 3 and 4). More Lewis acidic bromozinc salts **1D** and **1E** showed rather low enantioselection (Entries 1, 5, and 6). The influence of the ester group in bis(methylzinc) salt of tartrate was also investigated. The use of the esters derived from primary alcohols **1F** and **1G** afforded the product **4aa** with lower selectivities (Entries 7 and 8). It was found that *t*-butyl ester was the best choice to afford the *N*-hydroxylamine **4aa** with 82% ee (Entry 9).

Table 1. Asymmetric addition of alkynylzinc reagents to **2a**



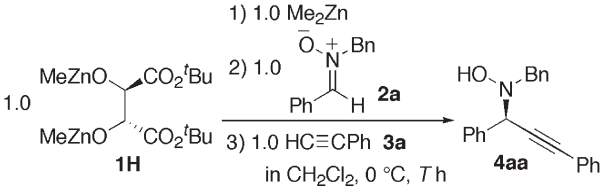
Entry	M^1	M^2	R^1	**1**	R^2	Yield/%	ee/%[a]
1	ZnEt	ZnEt	^{i}Pr	**A**	Et	74	73
2	Zn^{i}Pr	Zn^{i}Pr	^{i}Pr	**B**	^{i}Pr	58	73
3	ZnMe	ZnMe	^{i}Pr	**C**	Me	86	78
4	ZnMe	ZnMe	^{i}Pr	**C**	Et	88	78
5	ZnBr	ZnBr	^{i}Pr	**D**	Et	48	7[b]
6	ZnBr	ZnEt	^{i}Pr	**E**	Et	61	11
7	ZnMe	ZnMe	Me	**F**	Me	83	47
8	ZnMe	ZnMe	Et	**G**	Me	77	60
9	ZnMe	ZnMe	^{t}Bu	**H**	Me	89	82

[a]Enantioselectivities were determined by HPLC analysis (Daicel Chiralcel OD-H). [b](*S*)-Enantiomer was mainly obtained.

Next, in order to confirm how the reaction proceeded, the time course of the reaction corresponding to Entry 9 in Table 1 was observed (Table 2). Surprisingly, enantioselectivity was increased remarkably after around 8 h, suggesting that (*R*)-enantiomer was selectively produced after the induction time.

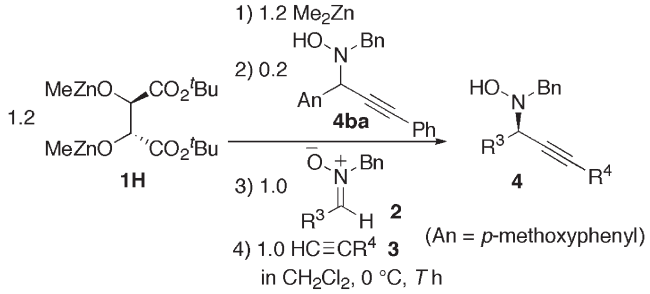
Based on this observation, if the product at initial stage of the reaction was added into the original reaction, the ee of the product could be enhanced without the induction time. In order to distinguish the product of the reaction and the additive, a product-like substrate was added to the reaction. Namely, a mixture of 1.2 molar amounts of bis(methylzinc) salt of di(*t*-butyl) (*R,R*)-tartrate (**1H**) and 1.2 molar amounts of dimethylzinc was treated with 0.2 molar amount of racemic *p*-methoxyphen-

Table 2. The time-course of the production of **4aa**



Entry	T/h	Yield/%	ee/%
1	2	2	—
2	4	10	47
3	8	13	49
4	19	70	79
5	24	89	82

Table 3. The asymmetric addition of alkynylzinc reagents to nitrones **2** in the presence of product-like additive



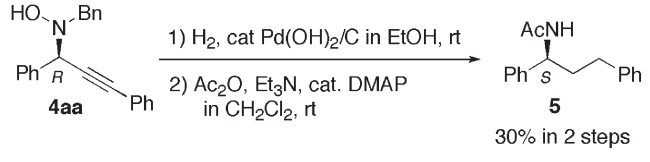
Entry	R^3	2	R^4	3	T/h	4	Yield[a]	ee	(Yield ee)[b]
1	Ph	**a**	Ph	**a**	18	**aa**	75	94[c]	(89 82)
2[d]	$^{p}MeOC_6H_4$	**b**	Ph	**a**	39	**ba**	80	92[e]	(70 74)
3	$^{p}BrC_6H_4$	**c**	Ph	**a**	18	**ca**	92	91[e]	(57 77)
4	$^{o}BrC_6H_4$	**d**	Ph	**a**	18	**da**	67	95[c]	(71 78)
5	Ph	**a**	$^{p}MeC_6H_4$	**b**	18	**ab**	70	86[e]	(58 76)
6[f]	Ph	**a**	$^{n}C_6H_{13}$	**c**	14	**ac**	62	79[c]	(48 57)

[a]Isolated yields/%. [b]Isolated yields/% and enantioselectivities/% ee in parentheses were the results of the reaction carried out without the product-like additive under the same conditions as that of Entry 9 in Table 1. [c]Enantioselectivity/% ee was determined by HPLC analysis (Daicel Chiralcel OJ-H). [d]The racemic **4aa** was used as an additive instead of the racemic **4ba**. [e]Enantioselectivity/% ee was determined by HPLC analysis (Daicel Chiralcel OD-H). [f]0.2 Molar amount of Me_2Zn was added in the step 1). Pre-reacted mixture of 1.0 molar amount of Me_2Zn and 1.0 molar amount of acetylene **3c** was added in the step 4); the reaction was carried out at rt.

yl-substituted product-like additive **4ba**,[10] followed by addition of 1.0 molar amount of the nitrone **2a** and phenylacetylene (**3a**). As expected, the enantioselectivity was enhanced from 82 to 94% ee (Table 3, Entry 1). The several asymmetric additions of acetylides to nitrones **2** in the presence of the product-like additive were also carried out to furnish the corresponding α-substituted propargylic *N*-hydroxylamines **4** with excellent enantioselectivities (Entries 2–6). By comparison with the reaction without the product-like additive (the results were shown in parentheses), the dramatic enhancement of the enantioselection was observed.

The absolute configuration of the propargylic *N*-hydroxylamine **4aa** was confirmed to be *R* by chemical correlation. Namely, **4aa** (76% ee) was transformed to the 1,3-diphenyl-1-propylamine derivative **5** ($[\alpha]_D^{25}$ −41 (c 0.23, MeOH), −55 (c 0.23, $CHCl_3$)), and its absolute configuration was determined to be *S* by the comparison with specific optical rotation of the known (*R*)-**5** (100% ee; $[\alpha]_D^{15}$ +54.4 (c 2.6, MeOH)) (Scheme 1).[11,12] The absolute configurations of other propargylic *N*-hydroxylamines **4** were tentatively assigned to be *R*.

As described above, an attractive asymmetric addition of alkynylzinc reagents to acyclic nitrones has been developed. By the addition of product-like substrate, the excellent enantioselectivities were realized.[13] Further investigation for the present peculiar asymmetric amplification by the racemic additive is now on progress in our laboratory.



Scheme 1.

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