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Catalytic asymmetric addition reactions leading to carbon–carbon bond formation: Phenyl and alkenyl transfer to aldehydes and alkynylation of α-imino esters*

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Abstract: Optically active tertiary aminonaphthol ligands were obtained by a new, convenient procedure and were found to catalyze the enantioselective alkenyl and phenyl transfer to aldehydes in high yields and excellent enantiomeric excesses (ee's). The catalytic asymmetric introduction of alkynyl functionality to α-amino acid derivatives was realized by the direct addition of terminal alkynes to α-imino ester in the presence of chiral copper(I) complex under mild reaction conditions.

Keywords: asymmetric; alkynylation; alkenylation; phenylation; catalyst.

INTRODUCTION

Over the past two decades, catalytic asymmetric addition reactions employing enolsilanes (aldol addition), allylstannanes (allylation), and dialkylzinc (alkylation) have proved to be remarkably effective, and products with excellent enantiomeric excesses (ee's) have been achieved for different types of C=X electrophiles. In contrast, catalytic asymmetric alkenyl, phenyl, and alkynyl transfers to carbonyl and imine compounds are less developed in spite of their importance in organic synthesis. There are two main obstacles for these synthetically very useful reactions: The synthesis of suitable transfer reagents is often difficult, and effective chiral catalysts are relatively rare.

Recently, a method of preparation of alkenylzinc reagents by the reaction of alkyne with borane followed by boron–zinc exchange [1] and a protocol for the generation of aryl nucleophile using aryl boronic acids as aryl sources [2] have been developed by Oppolzer et al. and Bolm et al., respectively. These new methods provide reliable and inexpensive approaches to the production of alkenyl and aryl nucleophiles. In our study, we used these methods to prepare transfer reagents for the addition of alkenyl and phenyl groups to aldehydes. Chiral active tertiary aminonaphthols were found to be highly effective ligands for the asymmetric addition reactions.

Optically active α-alkynyl α-amino acid derivatives are a special class of nonproteinogenic amino acids which possess important biological activities. However, from a synthetic standpoint, the α-alkynyl α-amino acid derivatives are challenging structures to prepare. Up to now, only a few noncatalytic methods employing alkynilides have been found to be successful [3,4]. Our aim is to develop a new

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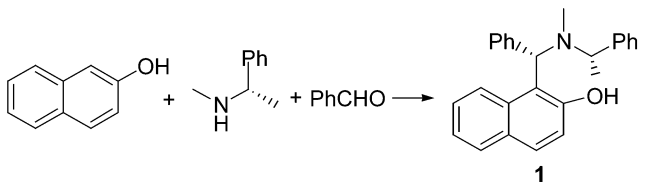
strategy of adding terminal alkynes to α-imino ester to realize the catalytic asymmetric synthesis of α-alkynyl α-amino acid derivatives.

CATALYTIC ASYMMETRIC ALKENYL TRANSFER TO ALDEHYDES

The asymmetric alkenylation of aldehydes affords useful chiral allyl alcohols. The search for efficient chiral ligands to generate high enantioselectivities in the alkenylations of different types of aldehydes is an important challenge in this area. For the practical applications of useful catalytic asymmetric synthesis, it is highly desirable to develop convenient methods for the preparation of effective chiral ligands.

Pure enantiomers of tertiary aminonaphthols are an important class of amino alcohol ligands and different strategies have been used for their preparation, e.g., resolution and selective alkylation of the corresponding secondary amine [5,6]. In this study, we developed a new and one-step method for the practical synthesis of optically active tertiary aminonaphthol **1**, which was found to be high activities and enantioselective (giving products in up to 99 % ee) in the alkenylation of various aldehydes [7].

In our attempt of the Mannich-type aminoalkylation of 2-naphthol, we found that the direct condensation of benzadehyde with 2-naphthol and (*S*)-(–)-*N*-α-dimethylbenzylamine without any solvent (Scheme 1) proceeded smoothly to give only one diastereomer of the tertiary aminonaphthol **1** exclusively at room temperature. The enantiomerically pure compound **1** was easily obtained by simply adding methanol to the crude reaction mixture, and the precipitated product could be used directly in the asymmetric alkenylzinc addition reactions without any further purification. The operational simplicity of this synthetic methodology makes it possible to synthesize chiral ligands on a large scale.

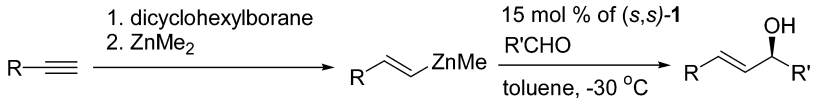


Scheme 1 One-step synthesis of ligand **1**.

The alkenylzinc reagents used in our study was prepared using a method developed by Oppolzer et al. [1]. The results of asymmetric alkenylation of aldehydes in the presence of chiral ligand **1** are summarized in Table 1.

As shown in Table 1, high ee's and isolated yields were obtained for a variety of aliphatic and aromatic aldehydes. Aliphatic aldehydes, such as cyclohexylcarbaldehyde and isobutyraldehyde, gave somewhat higher yields than aromatic aldehydes (entries 1–3). The electron-rich *m*-methoxybenzaldehyde and the electron-poor *m*-bromobenzaldehyde provided similar product ee's, while *o*-substituted benzaldehydes gave the best ee's.

Table 1 Alkenylzinc addition to a variety of aldehydes catalyzed by **1**[a].



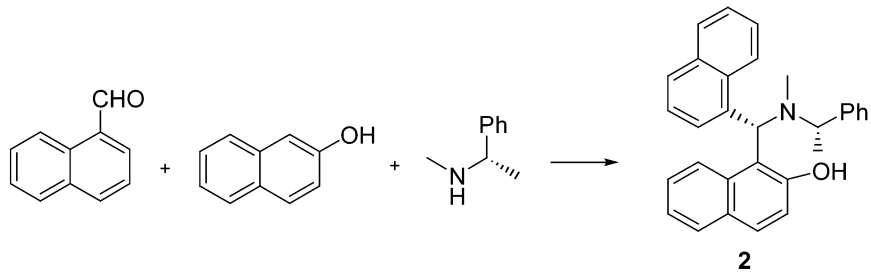
Entry	R	R'	Yield (%)[b]	ee (%)[c]
1	$Ph(CH_2)_2$	*c*-C_6H_{11}	93	95
2	$Ph(CH_2)_2$	*c*-C_6H_{11}	95	95
3	$Ph(CH_2)_2$	*i*-Pr	94	94
4	*n*-C_4H_9	phenyl	90	97
5	*n*-C_4H_9	*p*-Br-phenyl	89	94
6	*n*-C_4H_9	*p*-NO_2-phenyl	79	95
7	*n*-C_4H_9	*o*-NO_2-phenyl	77	98
8	*n*-C_4H_9	*o*-Cl-phenyl	90	>99
9	*n*-C_4H_9	*o*-Br-phenyl	87	98
10[d]	*n*-C_4H_9	*o*-Br-phenyl	84	96
11	*n*-C_4H_9	*m*-OMe-phenyl	91	94
12	*n*-C_4H_9	*m*-Br-phenyl	92	94

[a]2 equiv alkenylzinc reagent was used.
[b]Isolated yield.
[c]Determined by HPLC with chiral columns.
[d]$ZnEt_2$ was used in transmetallation instead of $ZnMe_2$.

CATALYTIC ASYMMETRIC PHENYL TRANSFER TO AROMATIC ALDEHYDES

Two conceptually different approaches have been used in the synthesis of chiral diarylmethanols, namely (1) asymmetric reduction of the corresponding unsymmetrical diaryl ketones [8–10], and (2) enantioselective phenyl transfer to aromatic aldehydes. In most previously reported preparations for the chiral ligands used in phenyl transfer reactions, multi-step syntheses are required [11]. Herein, we report a highly convenient method of using a new, easily prepared chiral tertiary aminonaphthol **2** as ligand [12].

A preliminary study was performed to test the catalytic property of the known ligand **1** in the phenyl transfer reaction to *p*-chlorobenzaldehyde. The nucleophile was preformed from phenylboronic acid and diethylzinc according to Bolm's protocol and 89 % ee was obtained when the reaction was performed at –10 °C in toluene. With this encouraging result, attention was turned to designing a new optically active tertiary aminonaphthol ligand for this reaction. We surmised that the attachment of a bulkier group at the new chiral center should favor selection of a conformationally more restricted transition state, which should be beneficial for stereochemical induction. The one-step procedure for the preparation of **1** was adopted to synthesize ligand **2** (Scheme 2). Up to 50 g of **2** can be prepared in one batch, which underscores the practicality of this method.

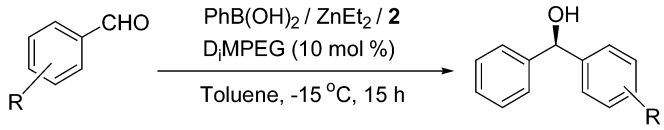


Scheme 2 One-step synthesis of ligand **2**.

Ligand **2** induced a higher enantioselectivity than **1** in the catalytic phenyl transfer reaction to *p*-chlorobenzaldehyde under the same conditions (Table 2, entry 1), which was in line with our anticipation. Table 2 summarized the results of asymmetric phenyl transfer to a variety of aryl aldehydes catalyzed by **2** to provide the corresponding chiral diarylmethanols with high ee's and yields. Even for *ortho*-substituted benzaldehydes, which are problematic with some other catalyst-ligand systems, high ee was achieved. Particularly noteworthy is that (*S*)-*o*-methyl benzhydrol, which was obtained in 99 % ee, is the direct precursor of orphenadrine, an anticholinergic and antihistaminic agent.

Another advantage of **2** is that its enantiomer could be easily synthesized from the equally inexpensive (*R*)-(–)-*N*-α-dimethylbenzylamine. Hence, both enantiomers of the diarylmethanols are accessible (Table 2, entry 9 vs. 10).

Table 2 Phenyl transfer to aromatic aldehydes catalyzed by **2**.

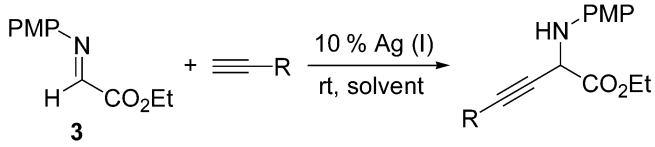


Entry	R	(*S*, *S*)-**2** (mol %)	Yield (%)[a]	ee (%)[b]
1	*p*-Cl	(16)	90	94
2	*p*-Cl	(8)	89	92
3	*o*-Cl	(16)	93	97
4	*o*-Cl	(8)	91	97
5	*o*-F	(8)	93	97
6	*o*-Br	(8)	90	97
7	*o*-Me	(8)	93	96
8[c]	*o*-Me	(8)	87	97
9	*o*-Me	(8)	94	98
10	*o*-Me	(8)	95	98
11[c]	*o*-Me	(8)	90	99
12	*m*-Me	(16)	87	95
13	*p*-Br	(16)	90	94
14	p-Me	(16)	93	94

[a]Isolated yield.
[b]Determined by HPLC with chiral columns. All products were of *R*-configuration, except for that in entry 10: (*R*,*R*)-**2** was used as catalyst to give the product with *S*-configuration.
[c]$ZnMe_2$ was used instead of $ZnEt_2$.

CATALYTIC ASYMMETRIC ALKYNYLATION OF α-IMINO ESTER

Recently, we reported the successful alkynylation of α-imino ester via the direct addition of terminal alkynes to α-imino ester 3 in the presence of Ag(I) salts under mild reaction conditions (Scheme 3 and ref. [13]). In this novel process, a new bond between an sp^3 carbon and an sp carbon is formed. This reaction is atom economical, as the nucleophile is directly generated.

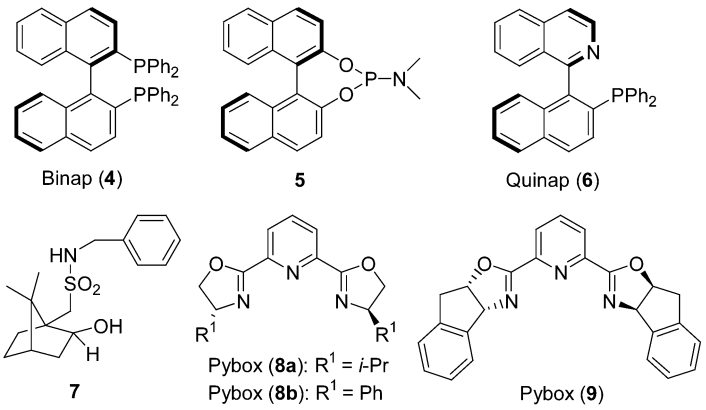


Scheme 3 Ag(I)-catalyzed alkynylation of α-imino ester.

Capitalizing on this method, we envisioned that the corresponding asymmetric version could be realized by using an appropriate chiral ligand [14]. The asymmetric addition of 4-phenyl-1-butyne to α-imino ester **3** was explored in the presence of AgOTf or $AgNO_3$ and an additional ligand, respectively. However, it turned out to be unsuccessful when a series of chiral ligands including aminophosphanes, diphosphanes, and pybox were tested. All of the experiments resulted in extremely low conversions and essentially no enantioselectivity.

We then switched our efforts to other transition metals such as IrCl·2COD, $Zn(OTf)_2$, $ZnCl_2$, $Sc(OTf)_3$ $CuPF_6$·4MeCN, CuOTf·$0.5C_6H_6$, $Cu(OTf)_2$, CuCl, CuBr, CuO_2, and CuOAc, some of which have been reported to lead the formation of metal alkynilides [15–23]. In the investigation of 4-phenyl-1-butyne addition to α-imino ester **3**, the desired product was obtained in good yields when using $CuPF_6$·4MeCN and CuOTf·$0.5C_6H_6$ as catalysts. Other copper complexes showed much lower or even undetectable catalytic activity.

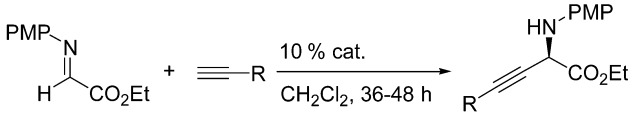
These interesting results led us to examine the effect of a variety of chiral ligands (Scheme 4) in $CuPF_6$·4MeCN-catalyzed asymmetric addition of 4-phenyl-1-butyne to α-imino ester **3** in CH_2Cl_2. Encouragingly, although the reaction rates suffered noticeably with the use of BINAP and QUINAP [23] as chiral ligands, different degrees of ligand acceleration were observed when employing **5**, **7**, and pybox (**8a**) as ligands and the addition reaction in the presence of $CuPF_6$·4MeCN/**8a** furnished target with promising enantioselectivity (59 % ee) and chemical yield (73 % yield). Further investigation involved the addition of amine bases and the use of other copper sources and structurally different pybox ligands. These optimizations led to the preferred conditions, using CuOTf·$0.5C_6H_6$ (10 mol %) as metal source, conformationally more restricted pybox (**9**) (10 mol %) as chiral ligand and $PMPNH_2$ (10 mol % as additive at −10 °C, which afforded desired product in 90 % yield and 85 % ee.

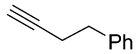
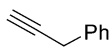
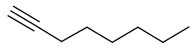
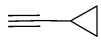
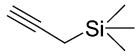
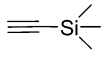


Scheme 4 Chiral ligands for screen in alkynylation of α-imino ester.

The direct alkynylation of α-imino ester **1** with a spectrum of terminal alkynes was performed under the optimized conditions, and the representative results were summarized in Table 3. In a like manner for the addition of 4-phenyl-1-butyne (entry 1), the addition reactions of 3-phenyl propyne (entry 2), 1-octyne (entry 3), and cyclopropylacetylene (entry 4) provided the corresponding alkynylation products in good yields and ee's. Whereas, alkynes with bulky substituted group next to the triple bond, such as trimethylsilyacetylene (entry 6), led to lower reaction rate and enantioselectivity.

Table 3 Alkynylation of α-imino ester catalyzed by $CuOTf{\cdot}0.5C_6H_6$/**9**.



Entry	Alkyne	Yield (%)[a]	ee (%)
1		90	85
2		92	83
3		89	91
4		92	79
5		63	77
6		55	48

[a]Isolated yields.

Noticeably, the present cyclopropylacetylene addition to α-imino ester **3** (entry 4) represents a new direct and convenient access to α-amino acid derivatives containing conformationally constrained cyclopropane rings, which have recently attracted much attention because of their important biological activities [24–28].

CONCLUSION

We described a successful application of chiral tertiary aminonaphthols in the enantioselective alkenylation and phenylation of aldehydes. Chiral secondary amine (*S*)-(–)-*N*-α-dimethylbenzylamine was for the first time used in the Mannich-type aminoalkylation of 2-naphthol to afford an efficient, one-step method for the preparation of the optically active tertiary aminonaphthol ligands. The simple and environmentally friendly operational procedure, coupled with the use of inexpensive reagents, render this synthetic method amenable to a large-scale application.

We also demonstrated the first catalytic synthesis of enantiomerically enriched α-alkynyl α-amino acid derivatives by realizing the direct asymmetric alkynylation of α-imino ester. Taking into account the combination of desirable features, such as high potential to generate structural variety, truly atom-economical, and readily available starting materials, simple experimental procedures as well as mild reaction conditions, this catalytic system is expected to provide an excellent opportunity for applications in the increasingly important protein engineering and peptide-based pharmaceutical research.

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