Asymmetric addition of 1-ethynylcyclohexene to both aromatic and heteroaromatic ketones catalyzed by a chiral Schiff base–zinc complex†

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The evaluation of a chiral Schiff base ligand in the zinc-catalyzed asymmetric addition of 1-ethynylcyclohexene to both aromatic and heteroaromatic ketones is reported (with up to 83% enantioselectivity and up to 88% isolated yield).

The asymmetric addition of metalated terminal alkynes to carbonyls is one of the most important methods for producing chiral propargylic alcohols. The resulting optically active propargylic alcohols are versatile building blocks for the synthesis of many natural products and pharmaceuticals.[1] In recent years, asymmetric addition of terminal alkynes to aldehydes has been studied extensively.[2] Comparatively, asymmetric addition of alkynes to ketones is much more complicated because of the inertness of ketones and controlled facial stereoselectivity.[3]

The first general method that allowed the enantioselective addition of acetylenes to unactivated ketones was introduced by Cozzi.[4] He employed Salen-metal complexes **1** (Fig. 1) as the bifunctional Lewis acid–Lewis base catalyst. However this protocol was proved to be more effective with aliphatic ketones. Another pioneering work was done by Chan *et al.*[5] They found that the coordinated complexes of chiral camphorsulfonamide ligand **2** (Fig. 1) and a strong Lewis acid $Cu(OTf)_2$ was very efficient in the addition of terminal phenylacetylene to aromatic ketones with up to 97% ee. Almost at the same time, Cozzi[6] and our group[7d] developed a practical protocol using commercially available BINOL as ligand **3** (Fig. 1) and good to excellent enantioselectivities were achieved. Recently we have reported that an easily prepared Schiff-base amino alcohol ligand **4** (Fig. 1) is an outstanding chiral director in the asymmetric addition of phenylacetylene to aromatic ketones.[7j] When the loading of **4** was 1 mol%, up to 95% ee value was obtained.

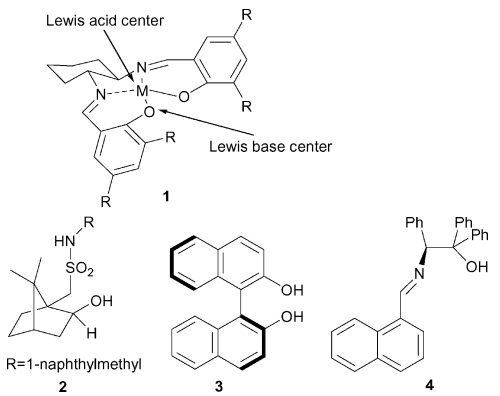

Fig. 1 Structures of ligands for the asymmetric alkynylation of ketones.

For possible further transformations of the alkene group, such as epoxidation, hydroxylation, ozonolysis, addition of carbenes, the asymmetric addition of 1-ethynylcyclohexene to aromatic and heteroaromatic ketones should have more potential applications than phenylacetylene for the synthesis of complex bioactive natural products. However, to our knowledge, the addition of functionalized alkynes to ketones is a rather undeveloped field, and the catalytic asymmetric addition of 1-ethynylcyclohexene to unactivated aromatic and heteroaromatic ketones has not been reported.

The reaction products of heteroaromatic carbonyls with alkynes are very useful in the synthesis of highly functionalized organic molecules. For example, 2-furyl alcohols can be transformed into 6-hydroxy-2-methyl-pyran-3(6*H*)-ones, important building blocks for the synthesis of bioactive natural products, through an oxidative rearrangement (Fig. 2).[8] On the other hand, the thiophene ring in the resulting thienyl alcohols can be desulfurized with Raney nickel acting as a masked four-carbon synthon (Fig. 2).[9] Recently, Pedro *et al.* reported the alkynylation of furane- and thiophenecarbaldehydes catalyzed by mandelamide-zinc complexes.[10] However, to our knowledge, the alkynylation of 2-acetylfuran and 2-acetylthiophene has not been explored and remains an interesting challenging reaction.

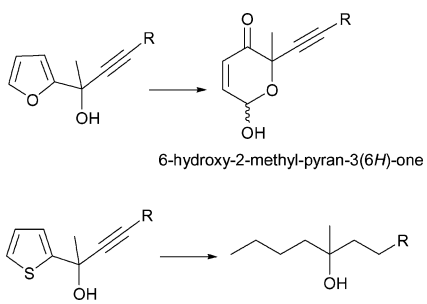

Fig. 2 Modification of heteroaromatic propargylic alcohols.

In this paper, we wish to report the use of Schiff-base amino alcohol **4** as a chiral ligand in the alkynylation of both unactivated aromatic and heteroaromatic ketones with 1-ethynylcyclohexene.

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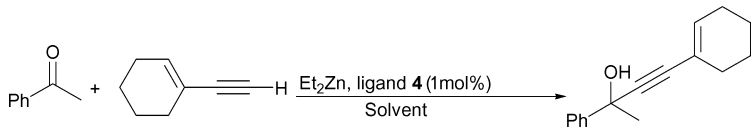
Table 1 Asymmetric addition of 1-ethynylcyclohexene to acetophenone promoted by ligand **4** (1 mol%)



Entry	Solvent	T/°C	Time/h[a]	Et_2Zn/mL[b]	Yield (%)[c]	Ee (%)[d]
1	Hexane	rt	2	0.75	39	57
2	Hexane	rt	4	0.75	50	63
3	Hexane	rt	6	0.75	52	65
4	CH_2Cl_2	rt	6	0.75	21	3
5	Toluene	rt	6	0.75	55	34
6	Hexane	rt	6	0.50	49	59
7	Hexane	rt	6	1.0	60	64
8	Hexane	−18	6	0.75	48	79

[a] Reaction times of 1-ethynylcyclohexene with Et_2Zn before the addition of acetophenone (0.25 mmol). [b] 1.0 M Et_2Zn in hexane, the amount of Et_2Zn used in entries 1–5 and 8 is 3 equiv. [c] Yields of isolated products, the reaction times after the addition of acetophenone were 24 hours. [d] The enantiomeric excess was determined by HPLC (Chiralcel OD-H column, IPA–hexane = 1 : 120, 228.5 nm).

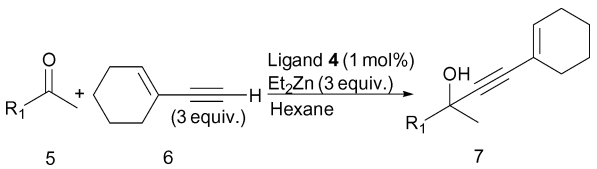
Preliminary studies were carried out with the model reaction of acetophenone and 1-ethynylcyclohexene. The reactions were conducted by a procedure similar to that with phenylacetylene. The active zinc catalyst for these reactions was generated by the sequential treatment of chiral ligand **4** and Et_2Zn at room temperature, and then 1-ethynylcyclohexene was added and stirred for 2 hours to prepare the active zinc alkynylide. Finally, acetophenone was added to the resultant reaction mixtures at 0 °C, and the reaction mixture was stirred for several hours at room temperature. Under these conditions, the product was obtained only in a low yield and with low enantioselectivity (Table 1, entry 1).

Further investigation revealed that prolonging the treatment of 1-ethynylcyclohexene with Et_2Zn in the presence of ligand **4** at room temperature before the addition of acetophenone led to the desired product in moderate yield and with increased enantioselectivity (Table 1, entries 2 and 3).

The solvent effects were also examined in this reaction, for example, the reaction proceeded readily in hexane with good results, but the polar solvent CH_2Cl_2 led to a practically racemic result (3% ee; Table 1, entry 4). Increasing the amount of Et_2Zn from 2 equivalents to 3 equivalents showed improvement in the enantiomeric excess of the product (Table 1, entry 6 and 3). The use of low temperatures slowed the reaction down, but increased the enantioselectivity (Table 1, entry 8).

Under the optimized reaction conditions of entry 8 (Table 1), ligand **4** was employed to catalyze the asymmetric addition of 1-ethynylcyclohexene to both aromatic and heteroaromatic ketones. The results are summarized in Table 2. For most aromatic ketones, the enantiomeric excess of the product was in the range 71–83% (Table 2, entries 1–9). Among them, 2-naphthacetophenone gave the best enantiomeric excess (83% ee; Table 2, entry 3). From Table 2, it can be seen that the yields for the addition to acetophenone derivatives were relatively low compared with the case of the furan or thiophene derivative. This could be explained by the increased electron density of the furan or thiophene derivative, which significantly enhanced the coordination of the carbonyls to the catalyst. As we know, furan or thiophene derivatives have one electron-rich atom (O, or S). On the other hand, they have 1 less ring atom than benzene to hold the same number of π

Table 2 Asymmetric additions of 1-ethynylcyclohexene to both aromatic and heteroaromatic ketones promoted by ligand **4** (1 mol%)[a,b,e]



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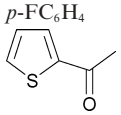
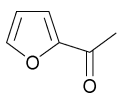
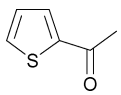
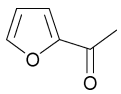
Entry	R_1	Product	Yield (%)[c]	Ee (%)[d]
1	Ph	**7a**	55	79
2	*o*-FC_6H_4	**7b**	62	81
3	2-Naphthyl	**7c**	63	83
4	*m*-BrC_6H_4	**7d**	59	75
5	*m*-MeC_6H_4	**7e**	63	80
6	*p*-$MeOC_6H_4$	**7f**	63	82
7	*p*-MeC_6H_4	**7g**	51	74
8	*p*-ClC_6H_4	**7h**	49	74
9	*p*-FC_6H_4	**7i**	45	71
10		**7j**	88	80
11		**7k**	85	65
12[f]		**7l**	66	83
13[f]		**7m**	70	67

[a] Ligand–ketones–Et_2Zn–1-ethynylcyclohexene = 0.01 : 1 : 3 : 3. [b] All the reactions conducted at −18 Å in 1 mL hexane. [c] Yields of isolated products. [d] The enantiomeric excess was determined by HPLC (see ESI†). [e] All the reactions were carried out for 48 hours. [f] The substrate is phenylacetylene.

electrons (6). In the asymmetric additions of 1-ethynylcyclohexene to 2-acetylthiophene and 2-acetylfuran, high yields were achieved (88 and 85% yield, respectively; Table 2, entries 10 and 11). We also studied the asymmetric additions of phenylacetylene to 2-acetylfuran and 2-acetylthiophene. Good enantioselectivities (80 and 83% ee, respectively; Table 2, entries 10 and 12) were obtained in the additions of both alkynes to 2-acetylthiophene.

In summary, we have evaluated our new chiral Schiff-base amino alcohol ligand **4** in zinc-complex catalyzed asymmetric reactions of 1-ethynylcyclohexene with both aromatic and heteroaromatic ketones. When the loading of **4** was 1 mol%, up to 83% ee value was obtained. The promotion of the reaction required no other metal, other than Et_2Zn, and the alkynylzinc does not need to be prepared in advance.

Studies are currently underway to improve the enantioselectivities that can be obtained with this new type of exceptionally promising chiral Schiff-base amino alcohol ligand, in various metal-catalyzed asymmetric processes, by screening within various amino acid derived Schiff-base amino alcohols.

Acknowledgements

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