Asymmetric Addition to Ketones

Enantioselective Alkynylation of Ketones Catalyzed by Zn(Salen) Complexes**

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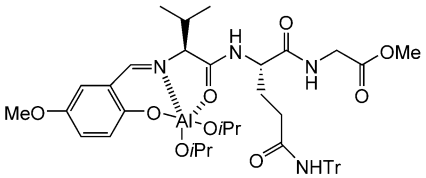
In recent years asymmetric catalysis has reached an impressive level of complexity.[1] However, there are still open challenges in the area of asymmetric catalysis, such as the development of environmentally safe methodologies and the use of substrates until now regarded as unreactive. In particular, ketones remain a great challenge for the state of the art of asymmetric methodologies.[2] Although effective methods have been described for the catalytic enantioselective reduction of ketones, few catalytic enantioselective C–C bond-forming reactions with ketones are known. Ketones are difficult substrates because of their low reactivity and because of the difficulty in controlling facial stereoselectivity.

Recently, pioneering studies were published on the enantioselective addition of allylstannane and diethylzinc to ketones.[2,3] To overcome the low reactivity of the substrate some important catalytic methodologies involve the concept of double activation. The substrate and the nucleophile are brought into close proximity by a system that is able to assemble them in an ordinate transition state.[4] Hoveyda and co-workers[5] and Shibasaki and co-workers[6] described the metal complexes **1** and **2**, respectively, in which the ligand is



able to direct the nucleophile onto the coordinated electrophile, as in an artificial enzyme. A catalytic amount of the metal complexes **1** and **2** was used to promote the addition of cyanide to ketones with the formation of a quaternary stereocenter with high enantioselectivity.

Salen complexes have remarkable properties and are able to act in a cooperative manner.[7] Moreover, a salen–metal complex can behave as a bifunctional Lewis acid–Lewis base catalyst (Figure 1).[8] As a result of efforts toward the development of new catalytic reactions with challenging substrates through the use of salen–metal complexes, herein the first general, facile, and effective method for the catalytic enantioselective addition of alkynes to ketones is reported.[9]

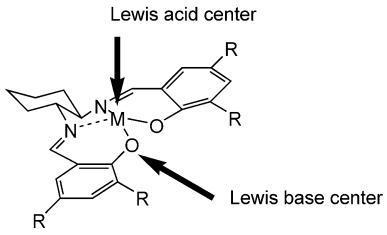


Figure 1. M(salen) as a bifunctional complex.

The addition of terminal alkynes to aldeydes and ketones through the formation of a zinc alkynide in situ has been described by Carreira and co-workers.[10] Impressive enantiomeric excesses were observed in the addition of alkynes to aldehydes in the presence of a substoichiometric amount of the inexpensive chiral ligand *N*-methylephedrine. The reaction appears to be general for substituted alkynes, although

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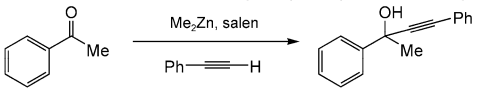
the use of aromatic aldehydes results in lower conversion. Remarkable results with reactive ketones (α-ketoesters) were reported by Jiang et al., who used a different chiral amine.[11] In an alternative method for the formation of the zinc alkynides, Chan and co-workers and Pu and co-workers used dialkyl zinc reagents, and carried out the enantioselective addition of phenylacetylene to aromatic and aliphatic aldehydes in the presence of binol (1,1′-binaphthalene-2,2′-diol), $Ti(OiPr)_4$, and a variety of additives.[12] In our attempts to use these methodologies, low reactivity and low enantioselectivity was observed in the case of acetophenone.

It was reasoned that Zn(salen)[8a,13] (M = Zn, Figure 1) could act as a bifunctional catalyst to enhance the reactivity of ketones toward the attack of zinc alkynides and were delighted to find that the salen complex promoted the addition of phenylacetylene to acetophenone. The model reaction of phenylacetylene with acetophenone was optimized by varying parameters such as solvent, temperature, mode of addition, preparation of the zinc alkynide, and quantity of salen added. The optimized protocol is very straightforward and uses commercially available starting materials. No particular conditions appear to be necessary for the formation of the active complex, and commercial anhydrous toluene was used for all the reactions. The zinc alkynide was prepared by stirring Me_2Zn and phenylacetylene for 1 hour at room temperature in toluene, then the salen was added to the reaction mixture.[14] Finally the ketone was added and the reaction mixture was stirred for several hours at room temperature (Table 1).

As indicated in Table 1, 20 mol% of the salen was required to guarantee sufficient reactivity, while 3 equivalents of the zinc phenylacetylide were used with respect to the ketone. The use of low temperatures slowed the reaction down considerably, and at −15 °C the reaction did not proceed at all. Upon increasing the reaction temperature to 50 °C, fast conversion was observed, but the enantioselectivity was inferior to that observed in other cases. A range of salen ligands were tested with the optimized protocol to increase the enantioselectivity of the reaction (see Supporting Infor-

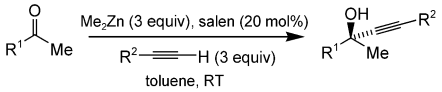
Table 1: Enantioselective addition of phenylacetylene to acetophenone.[a]

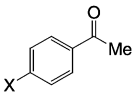
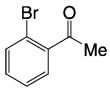
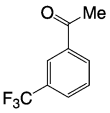
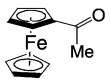
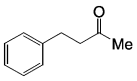


Entry	Salen [mol%]	Additive[b]	Yield [%][c]	*ee* [%][d]
1	10		40	62
2	20		72	61
3	20[e]		n.d.	51
4	20[f]		n.d.	50
5	20[g]		n.d.	53
6	20[h]		85	31
7	10	(*R*,*R*)-indanol	n.d.	39
8	10	(*R*,*R*)-binol	n.d.	30
9	10	dabco	n.d.	53
10	10	2,6-lutidine	n.d.	44
11	20[i]		0	–
12	20[j]		n.d.	42

[a] All the reactions, unless otherwise stated, were carried out in toluene for 96 h at room temperature with the zinc alkynide (3 equiv; prepared by mixing phenylacetylene and Me_2Zn). [b] The additive (10 mol%) was added after the salen to the reaction mixture. [c] Yield after chromatographic purification; n.d. = not determined. [d] The enantiomeric excess was determined by chiral HPLC analysis; see Supporting Information for details. [e] The reaction was performed in Et_2O. [f] The reaction was performed in CH_2Cl_2. [g] The reaction was performed in hexane. [h] The reaction was performed at 50 °C for 48 h. [i] The reaction was performed at −15 °C for 96 h. [j] The zinc alkynide was prepared according to Pu and co-workers; see reference [12c]. dabco = 1,4-diazabicyclo[2.2.2]octane.

Table 2: Enantioselective addition of substituted alkynes to aliphatic and aromatic ketones.[a]



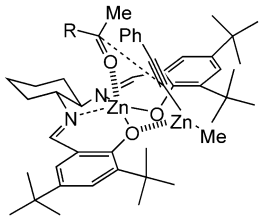
Entry	Ketone	Alkyne	Yield [%][b]	*ee* [%][c]
				
1	X = F	≡—Ph	53	57
2	X = Cl	≡—Ph	55	53
3	X = Br	≡—Ph	78	53
4	X = NO_2	≡—Ph	75	53
5	X = *t*Bu	≡—Ph	45	66
6		≡—Ph	50	70
7		≡—Ph	81	61
8		≡—Ph	40	62
9		≡—Ph	89	32
10		≡—Ph	40	50
11		≡—Ph	84	57
12		≡—Ph	89	80
13		≡—Ph	52	69
14		≡—$SiMe_3$	75	64
15		≡—$SiMe_3$	40[d]	81
16		≡—Cl	40	80

[a] All the reactions were carried out for 36 h for aliphatic ketones and 96 h for aromatic ketones. [b] Yield of isolated product. [c] The enantiomeric excess was determined by GC or HPLC; see Supporting Information for details. [d] Volatile compound.

mation). In common with many other reactions promoted by salen–metal complexes, the commercially available compound (*R*,*R*)-(−)*N*,*N*′-bis(3,5-di-*tert*-butylsalicilidene)-1,2-cyclohexanediamine (Figure 1, R = *t*Bu) appears to be the most suitable chiral ligand for this reaction. A variety of additives, such as bases, amino alcohols, alcohols, phenols, and other chiral ligands, such as binol, taddol (1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-L-threitol), and binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) were also added in varying amounts to the reaction mixture, but with no improvement in the enantiomeric excess of the product.[15]

The optimized protocol was used for a range of aromatic and aliphatic ketones (Table 2).[16] The reactions showed good functional-group compatibility and strong deactivating groups such as NO_2 could be present.[17] In general, aromatic ketones proved less reactive than aliphatic ketones, and aromatic ketones that bear an electron-donating group reacted slowly with phenylacetylene. The enantiomeric excess of the product seems to depend on how sterically hindered the ketone is, whereas electronic effects play only a minor role. For all aromatic ketones studied that bear substituents in the 2-, 3-, or 4-position, the enantiomeric excess of the product was in the range 53–70%. The reaction demonstrates a useful level of selectivity with hindered ketones. For all substituted alkynes used in the reaction with *tert*-butyl methyl ketone, the enantiomeric excess of the isolated product was 80–81%. The absolute configuration of the compounds obtained from the addition of trimethylsilylacetylene to aliphatic ketones was established as *S* by comparison of optical rotation values with that reported for a known compound.[18] As there is no reason to believe that the other alkynes react differently, the addition of alkynes is assumed to occur to the *Re* face of the ketones.

Although the mechanism of this reaction has not yet been studied, the correlation between enantioselectivity and the enantiomeric excess of the ligand (nonlinear effect) provided some useful information about the catalyst system. The addition of phenylacetylene to *tert*-butyl methyl ketone was studied with salen of varying enantiomeric purity.[19] Within the limits of experimental error, a linear correlation was found between the enantiomeric excess of the salen ligand and that of the product (Figure 2). This correlation strongly indicates that only one molecule of the salen catalyst is involved in the enantiodifferentiating step, thus suggesting that a Lewis acid–Lewis base double activation promoted by a single salen molecule takes place in the transition state, as proposed in **3**.[20]



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In summary, the first general catalytic enantioselective addition of terminal alkynes to ketones in the presence of a commercially available chiral ligand was described. Further studies to improve the selectivity and applicability of this methodology through the design of more selective salen ligands are underway.

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Keywords: alkynes · asymmetric catalysis · ketones · salen · tertiary alcohols

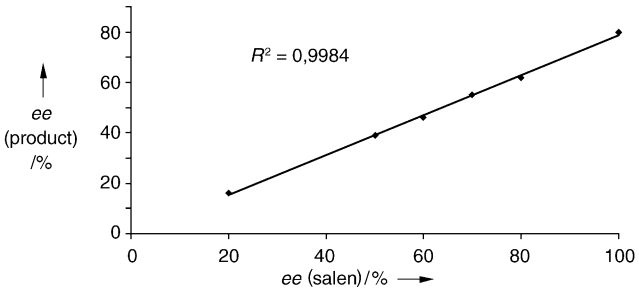

Figure 2. Absence of nonlinear effect in the Zn(salen)-mediated addition of phenylacetylene to *tert*-butyl methyl ketone. *R* = correlation coefficient.

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