Asymmetric Addition of Terminal Acetylenes to Aldehydes, Catalyzed by $Zn(OTf)_2$–Cinchona Alkaloid Complexes

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Abstract: Cinchona alkaloids in combination with zinc triflate catalyze the addition of acetylenes to aldehydes at room temperature with ee up to 89% for aliphatic aldehydes. Cinchonidine has proven to be the ligand of choice for the addition reaction whose outcome is demonstrated to be very sensitive to the alkaloid structure. Aromatic aldehydes are less reactive and give adducts of low optical purity. The more sterically hindered 2-bromo- and 2-nitrobenzaldehydes are considerably more reactive in the reaction as compared to their 4-substituted congeners.

Key words: addition reactions, aldehydes, alkaloids, alkynes, asymmetric catalysis

The addition of acetylenes to carbonyl compounds represents the most straightforward and atom economical approach to propargyl alcohols known so far. The importance of these compounds in academic research and in industrial applications is the major driving force for the constant development of this reaction. Among recent achievements in the field is the development of catalytic versions of this process.[1–8] However, most of these protocols still employ stoichiometric amounts[9] of organometallic reagents (mainly dimethyl or diethyl zinc) in order to generate the reactive metal acetylenides.[3,4,6–8] A breakthrough in this field was made by Carreira and coworkers who used zinc acetylenides generated in situ from zinc triflate and acetylenes for the addition to aldehydes.[10–15] Soon afterwards catalytic versions of this reaction were realized.[6,15–17] The use of the latter method does not only eliminate the inconvenient employment of already manufactured organometallic compounds, it also allows for a considerable decrease of the amounts of metal precursor. Although the price of $Zn(OTf)_2$ is slightly higher as compared to $ZnEt_2$,[2] the in situ generation of acetylenides is much more promising, especially in its catalytic versions. Moreover, recent stoichiometric modifications of this method have proven efficient for the addition of acetylenes to the keto functionality of α-keto esters.[18]

The most successful ligands used for the zinc triflate mediated addition of acetylenes to aldehydes are based on N,N-dialkylated α,β-amino alcohols, and particularly, high stereocontrol (up to 99% ee) is obtained with *N*-methylephedrine (Figure 1).[6,15–17]

Figure 1

Cinchona alkaloids (Figure 2) readily available from the chiral pool are among the least expensive representatives of N,N-dialkylated α,β-amino alcohols, and they have already found extensive use in various asymmetric catalytic applications.[19]

Although these alkaloids contain several stereogenic centers, the couples cinchonidine–cinchonine [**1**–**2**] and quinine–quinidine [**3**–**4**] are sometimes called pseudo-enantiomers due to the opposite configurations of the amino alcohol moieties. Recently, compounds **1**–**3** were employed as ligands in the $ZnEt_2$-mediated addition of phenylacetylene to carbonyl compounds.[3,5,20] In the case of benzaldehyde **1** and **3** gave low enantioselectivity[3,5]

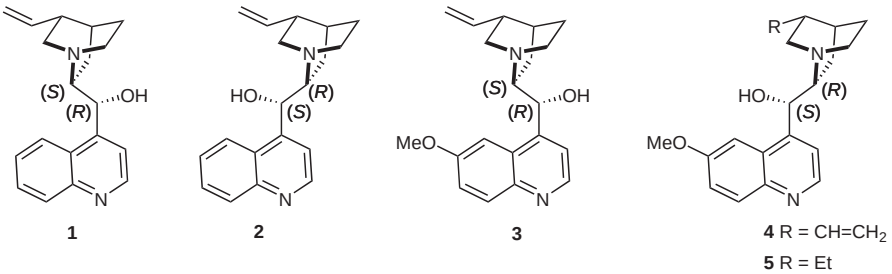

Figure 2

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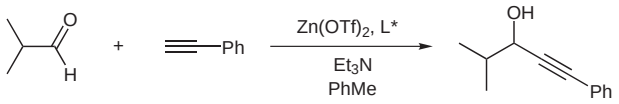
which, however, was dramatically improved by the addition of titanium isopropoxide.[3] The triethylaluminum-promoted addition of phenylacetylene to acetophenone in the presence of **3** as a ligand was reported to give up to 89% ee.[20]

In this communication we present results on the use of cinchona alkaloids as ligands in the $Zn(OTf)_2$-catalyzed addition of acetylenes to aldehydes.[21]

In an initial screening of ligands in the reaction between 2-methylpropionaldehyde and phenylacetylene (Scheme 1) catalyzed by $Zn(OTf)_2$, we found that ligand **1** gave the best result with respect to yield and enantioselectivity (Table 1).



Scheme 1

The influence of temperature on the reaction outcome strongly depended on the alkaloid structure. For instance, when **1** was employed as ligand, a decrease in reaction temperature from 60 °C to room temperature increased the enantiomeric excess of the product from 63% to 74%. Performing the reaction at 4 °C did not improve the selectivity. In contrast, alkaloids **2**, **4** and hydroquinidine (**5**) gave relatively poor enantioselectivity at 60 °C, and, more surprisingly, only racemic product was obtained with these ligands at room temperature. Interestingly, ligands **1** and **3**, differing only by the presence of a methoxy group in the quinoline ring, gave dramatically different results even though the substituent is positioned relatively distant from the amino alcohol moiety. These observations demonstrate an apparent high sensitivity in the chiral molecular recognition of the substrate by the catalytic complex, an effect, which must origin from the other stereogenic centers and/or the distal substituents.

Reduction of the catalyst loadings from 20 mol% to 10 mol% and 5 mol%, respectively, resulted in a considerable drop of yield, however, the enantioselectivity was almost unaffected (entries 11 and 12, Table 1). In contrast to the results obtained by Carreira and coworkers, who observed a significant drop of enantioselectivity when toluene was replaced by THF or dichloromethane,[11] we noticed only a small deterioration of the ee upon the change of reaction media (entries 13 and 14, Table 1).

Further, using **1** as a ligand, the reaction was extended to other aldehydes and acetylenes (Table 2). The increased steric encumbrance in 2,2-dimethylpropionaldehyde relative to 2-methylpropionaldehyde allowed for a significant improvement of the enantioselectivity in the phenylacetylene addition to the former aldehyde (entry 1, Table 2). Phenylacetylene addition to aromatic aldehydes gave lower yields and enantioselectivities as compared to their aliphatic counterparts. This might be due to the flat nature of the aromatic substituents, which makes them less distinguishable from hydrogens by the chiral catalytic complex as compared to the alkyl chains of aliphatic aldehydes. Thus, the more sophisticated three-dimensional architecture of the Zn–cinchona alkaloid complex has a stronger influence on the molecular recognition of the substrates as compared to the corresponding *N*-methylephedrine complex, which gives more or less similar stereochemical results for aliphatic and aromatic ketones.[11–13,17]

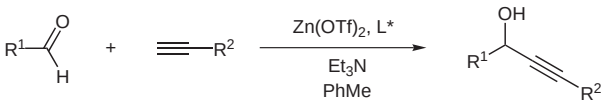
Table 1 Different Cinchona Alkaloids as Ligands in the Addition of Phenylacetylene to 2-Methylpropionaldehyde (Scheme 1)

Entry	Ligand[a]	Temp (°C)	Time (h)	Yield (%)	ee (%)[b]
1	**2**	60	6	70	–34
2	**4**	60	6	48	–26
3	**5**	r.t.	24	16	2
4	**4**	r.t.	24	–	n.d.
5	**3**	r.t.	24	3	29
6	**2**	r.t.	24	71	2
7	**1**	60	6	71	63
8	**1**	60	24	82	61
9	**1**	r.t.	24	**83**	**74**
10	**1**	4	27	61	73
11[c]	**1**	r.t.	24	56	72
12[d]	**1**	r.t.	24	42	69
13[e]	**1**	r.t.	24	69	70
14[f]	**1**	r.t.	24	60	67
15	**1**	r.t.	6	53	67

[a] 20 mol% $Zn(OTf)_2$ and 22 mol% ligand unless otherwise stated.
[b] Excess of the enantiomer with higher retention time was accepted as positive.
[c] Double loadings of substrates (i.e., 10 mol% of the catalyst).
[d] Fourfold loadings of substrates (i.e., 5 mol% of the catalyst).
[e] THF as a solvent.
[f] CH_2Cl_2 as a solvent.

The addition of phenylacetylene to benzaldehyde (Table 2, entry 4) employing ligand **2** resulted in a modest enantiodifferentiation (26% ee). However, in comparison to the low enantiocontrol (2% ee) obtained in the same reaction with 2-methylpropionaldehyde (Table 1, entry 6) the former result is most instructive. The close to racemic product mixture obtained in the reaction with 2-methylpropionaldehyde is clearly a result of poor discrimination between the enantiofaces of the substrate, rather than a difficulty in the formation of the catalytically active complex. The reactivity of different benzaldehydes was strongly influenced by the nature and position of the substituents on the aromatic ring. Surprisingly, the addition of phenylacetylene to the sterically more hindered carbonyl

Table 2 Addition of Phenylacetylene to Different Aldehydes Catalyzed by $Zn(OTf)_2$–Cinchona Alkaloid System



Entry	R^1	R^2	Ligand	Time (h)[a]	Yield (%)	ee (%)
1	*t*-Bu	Ph	**1**	24	61	89
2	Ph	Ph	**1**	24	26	27
3[b]	Ph	Ph	**1**	24	16	12
4	Ph	Ph	**2**	24	7	–26
5	4-MeO-C_6H_4-	Ph	**1**	24	Traces	n.d.
6	2-MeO-C_6H_4-	Ph	**1**	24	Traces	n.d.
7	4-Me-C_6H_4-	Ph	**1**		Traces	n.d.
8	4-NO_2-C_6H_4-	Ph	**1**	24	–	n.d.
9	3-NO_2-C_6H_4-	Ph	**1**	24	30[c]	25
10	2-NO_2-C_6H_4-	Ph	**1**	24	68[c]	22
11	2-NO_2-C_6H_4-	*n*-Bu	**1**	24	38[c]	56
12	4-Br-C_6H_4-	Ph	**1**	24	–	n.d.
13	2-Br-C_6H_4-	Ph	**1**	24	48[c]	64

[a] All the reactions were run at r.t.
[b] The reaction in the presence of 1 equiv Ti(*i*-PrO)$_4$.
[c] Conversion determined by ^{1}H NMR.

group in 2-bromo- and 2-nitrobenzaldehydes proceeded much easier than in their 4-substituted congeners. This behavior could be explained by a strong inductive effect from the 2-substituents. However, chelation assistance enforcing coordination of carbonyl oxygen to zinc, and hence activating the carbonyl group, is probably the main reason why 2-substituted derivatives are more reactive. Expectedly, due to the lower acidity of the acetylenic hydrogen, 1-hexyne showed considerably poorer reactivity as compared to phenylacetylene (cf. entries 10 and 11, Table 2). On the other hand, significantly higher enantioselectivity was obtained employing the alkyl-substituted acetylene. In contrast to the $ZnEt_2$-based alkynylation of aldehydes, the addition of Ti(*i*-PrO)$_4$ to the reaction mixture only deteriorated the reaction outcome (entry 3, Table 2).

In conclusion, we have demonstrated that cinchona alkaloids in combination with zinc triflate catalyze the addition of acetylenes to aldehydes, and the formed propargyl alcohols were obtained in up to 89% enantioselectivity. The activity and selectivity of the catalysts is very dependent on slight variations in the alkaloid structure. Distal stereogenic centers play a dramatic role in the enantiocontrol, making matched–mismatched behavior strongly pronounced. In addition, the enantiodifferentiation is apparently highly sensitive to the nature of the aldehydes and acetylenes.

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(21) In a typical experiment the reactions were run under conditions employed by Carreira and coworkers for catalytic addition of acetylenes to aldehydes in toluene.[16] $Zn(OTf)_2$ (0.036 g, 0.10 mmol, 20 mol%) was heated in a standard Radley reaction carousel test tube at 125 °C in vacuo (<1 mbar) for 5 h. After cooling the tube to r.t. and releasing vacuum the cinchona alkaloid was added (0.11 mmol, 22 mol%) and the mixture was evacuated for 0.5 h. To it was added dry toluene (0.5 mL) and Et_3N (0.025 g, 0.25 mmol), and the tube content was stirred for 2 h at r.t. Subsequent addition of acetylene (0.60 mmol) and stirring for 0.25 h at r.t. was followed by addition of aldehyde (0.50 mmol). The reaction was performed at r.t. or 60 °C (temperature and time are presented in Table 1 and Table 2). After the required reaction time, the reaction mixture was filtered through a plug of silica, using EtOAc as eluent, and the filtrate was evaporated in vacuo to give the product. The ee of the products was determined by chiral-phase HPLC analysis.