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Asymmetric Addition of Phenylacetylene to Aldehydes Catalyzed by β-Sulfonamide Alcohol-Titanium Complex

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Abstract: A series of β-sulfonamide alcohol ligands were synthesized from L-phenylalanine. Titanium complexes of these compounds were used to catalyze the asymmetric addition of phenylacetylene to a number of aldehydes. When the conditions were optimized, 20 mol % of ligand **8a** catalyzed the reaction with high enantioselectivity (up to 98% ee) and good yield (up to 92%). When a small amount of MeOH was added to the reaction as a modifier, as little as 5 mol % of ligand was required to efficiently catalyze the reaction under very mild conditions, resulting in an ee of up to 99% and good yield.

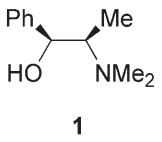
Keywords: asymmetric alkynylation; C–C bond formation; N,O ligands; sulfonamides; titanium; zinc

Introduction

Asymmetric carbon-carbon bond formation is an area of intense research in organic chemistry.[1] One of the most powerful methods for the catalytic asymmetric generation of carbon-carbon bonds is the enantioselective addition of organometallic reagents to aldehydes or ketones. In recent years there has been great interest in asymmetric catalytic addition reactions of terminal alkynes to aldehydes.[2,3] The acidity of a terminal alkynyl proton makes it easy to prepare alkynyl-metal reagents as good functional carbon nucleophiles and the resulting products, chiral propargylic alcohols, are important precursors to many chiral organic compounds.[4]

Carreira et al.[5] developed an efficient in situ method for the generation of zinc acetylides from terminal alkynes, utilizing $Zn(OTf)_2$, and an amine base *via* π-complex formation. They successfully used this method for the enantioselective alkynylation of an aliphatic aldehyde using *N*-methylephedrine (**1**; 22 mol %) as a catalyst. However, because of the strongly basic conditions, aromatic aldehydes may not be used (Carreira reported Cannizzaro reaction as a significant side reaction). Furthermore, the high temperatures used in the reaction may also limit the scope of the reaction.

Pu et al. reported[6] that the titanium complex of BINOL (**2**; 20 mol %) catalyzed the asymmetric alkynylation of aldehydes with high ee and good yield. They used a separate step for the preparation of the zinc acetylide by combining $ZnEt_2$ and the alkyne at high temperatures. Without this separate step, the ethyl addition product was the main product. Concurrently, Chan et al. reported[7] that the BINOL-Ti complex successfully catalyzed this asymmetric reaction in high ee with *N*-*p*-toluenesulfonylephedrine as the additive.



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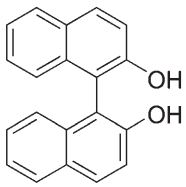

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The N–H group of sulfonamides is acidic. Unlike traditional metal amides (MNR_2), the sulfonamide nitrogen atom is a poor electron donor and the N–H group of the sulfonamide-Ti complex is a Lewis acid, owing to the highly electron-withdrawing nature of the sulfonyl group.[8] Amino alcohols derived from natural amino acids are among the best and most economical chiral ligands available.[9] We introduced the sulfonyl group to β-amino alcohols derived from amino acids to prepare β-sulfonamide alcohols.[10] As a result of the presence of acidic N–H and O–H groups, the titanium complex was readily formed from these compounds when they were combined with $Ti(O\text{-}i\text{-}Pr)_4$ under basic conditions.

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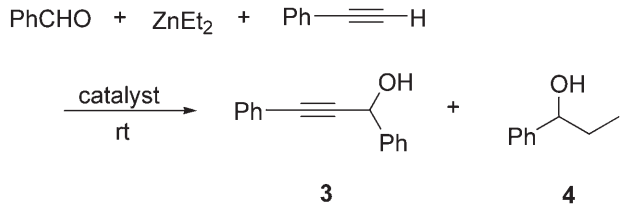
Initially, we expected these complexes to behave similarly to BINOL-Ti complexes, and that they could be straightforwardly applied to the enantioselective addition of phenylacetylene to aldehydes.[11] To our astonishment, this kind of titanium complex had a very different catalytic activity than the BINOL-Ti complex in this type of reaction. The separate step to prepare the zinc acetylide by combining $ZnEt_2$ and alkyne at high temperature was not required. After the conditions had been optimized, these ligands could efficiently catalyze the asymmetric alkynylation of aldehydes with high ees and high yields in one step.[12] Herein, we describe the details of our research.

Results and Discussion

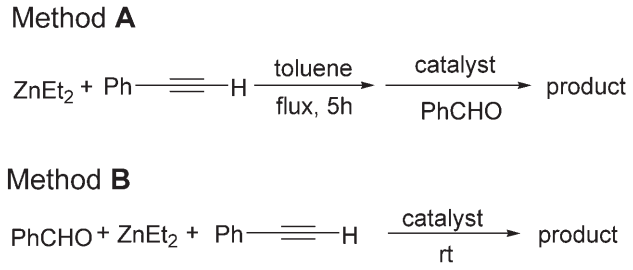
At room temperature, the reaction to produce the zinc acetylide directly by combining $ZnEt_2$ and alkyne is very slow. Hence, in the titanium-based catalytically induced asymmetric addition of alkynylzinc to aldehyde when the $ZnEt_2$, the alkyne and the aldehyde are combined together at room temperature, multiple products will result. When benzaldehyde is used as the representative substrate, two possible products would form: the alkynylzinc addition product **3**, and the ethylzinc addition product **4** (Scheme 1).



Scheme 1. Titanium-based catalyst may give two possible products.

In order to determine the effect of the catalyst on the selectivity of the two possible products, we used two different methods: **A**) pre-preparation of the alkynylzinc followed by addition of the aldehyde according to Pu's method and **B**) combination of $ZnEt_2$ (3 equivs.) with the alkyne (3 equivs.) and aldehyde (1 equiv.) at room temperature (Scheme 2). Using method **A**, we got a **3**/**4** ratio of > 98/2 (Table 1, entry 1). Following process **B**, compound **4** was the main product. Under conditions **B**, the ligand to metal ratio was varied from 1/1 to 1/5 (entries 2–6).

When BINOL and $Ti(O\text{-}i\text{-}Pr)_4$ were combined in the ratio of 1/1, the resulting (BINOLate)$Ti(O\text{-}i\text{-}Pr)_2$ is a stronger Lewis acid than at other ratios. In addition, the metal center is hardest.[13] Use of this catalyst resulted in the formation of nearly all **4** following completion of the reaction. However, when the ratio of the two catalyst compounds was increased, the Lewis acidity of the catalyst decreased and a small amount of compound **3** was formed. This result led us to question whether the metal's Lewis acidity or rigidity affected the reaction's selectivity.



Scheme 2. Addition of phenylacetylene to benzaldehyde by different methods.

Table 1. Addition of phenylacetylene to benzaldehyde by different methods.[a]

Entry	Method	Ligand	Ligand/$Ti(O\text{-}i\text{-}Pr)_4$[b]	**3**/**4**[c]
1	**A**	(*S*)-BINOL	1/3	98/2
2	**B**	(*S*)-BINOL	1/1	< 1/99
3	**B**	(*S*)-BINOL	1/2	< 1/99
4	**B**	(*S*)-BINOL	1/3	3/97
5	**B**	(*S*)-BINOL	1/4	5/95
6	**B**	(*S*)-BINOL	1/5	6/94
7	**B**	(+)-TADDOL	1/3	62/38

[a] Phenylacetylene:Et_2Zn:benzaldehyde = 3 : 3 : 1.
[b] Toluene as solvent and $Ti(O\text{-}i\text{-}Pr)_4$ was freshly distilled.
[c] The ratio of **3**/**4** was measured by a calibrated HPLC method.

TADDOL is another classical diol ligand, but the acidity of the hydroxy group in TADDOL is weaker than that of the BINOL hydroxy group. It forms a Ti complex when combined with $Ti(O\text{-}i\text{-}Pr)_4$.[14] The Lewis acidity of the resulting TADDOL-Ti complex is weaker than that of the BINOL-Ti complex and metal center is softer. We decided to employ this catalytic system in an effort to explore whether the Lewis acidity of the metal center influences the chemical selectivity. When this system was utilized following method **B**, we obtained products **3** and **4** in a ratio of 62/38 (entry 7).

Encouraged by above experimental results, we supposed that a weak Lewis acid catalyst prefers to promote addition of the alkyne to the aldehyde rather than addition of the ethyl group. Hence, in an effort to further study the effect of the relative strength of the Lewis acidic catalyst on the reaction, a weaker Lewis acid catalytic system was sought. In non-protonic solvents, the acidity of the sulfonamide hydrogen is much weaker than that of the hydroxy group in TADDOL or BINOL. In fact, it will not react with $Ti(O\text{-}i\text{-}Pr)_4$ in the absence of $ZnEt_2$.[8] Furthermore, the sulfonyl oxygen is chelated

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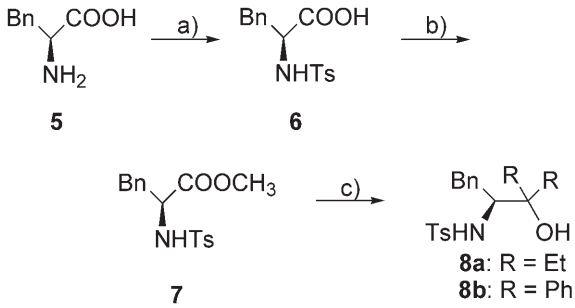
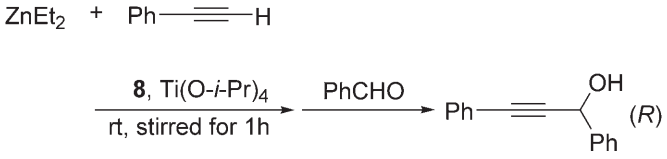


a) NaOH (2 equivs.), H_2O, TsCl (1 equiv.), Et_2O, rt, 24 h;
b) $SOCl_2$ (1.2 equivs.), MeOH, –30 °C, 30 min, then flux for 2 h;
c) RMgBr (5 equivs.), THF, rt, 24 h.

Scheme 3. Preparation of *p*-toluenesulfonylamino alcohol from L-Phe.

Method **C**



Scheme 4. Addition of phenylacetylene to benzaldehyde by method **C**.

to Ti, making the metal center much softer and its Lewis acidity weaker.[15]

We have synthesized two *N*-Ts sulfonamide alcohols (Ts = *p*-toluenesulfonyl), **8a** and **8b**, from L-phenylalanine[16] in three straightforward steps in overall yields of 67% and 62%, respectively (Scheme 3). When compound **8a** was utilized as catalyst (Table 2), following protocol **B**, a **3/4** product ratio of 93/7 was obtained (entry 1). An improved preparation method **C** was developed to optimize the selectivity of the reaction. Method **C** involves the initial mixing of $ZnEt_2$ and the alkyne at room temperature for one hour followed by the addition of the aldehyde. Using this procedure, we could get a **3/4** ratio > 99/1 (Scheme 4, entry 2). It was also determined that the amounts of phenylacetylene and $ZnEt_2$ also affect the reaction result. When the amounts of these compounds were reduced, more product **4** was obtained (entries 3 and 4). However, reducing the amount of ligand did not affect the yield of main product (entries 6 and 7).

These two sulfonamide ligands, **8a** and **8b**, were tested in the asymmetric addition of phenylacetylene to benzaldehyde by method **C**. Interestingly, compound **8b**, which has the bulkier, less flexible phenyl substituents at the hydroxy-bearing carbon atom, resulted in a lower enantioselectivity (Table 3, entry 1) than compound **8a**, which has the more flexible ethyl substituents (Table 3, entry 2). We varied the amount of Ti(O-*i*-Pr)$_4$ in the reaction and found that the best ee was obtained when the **8a**/Ti(O-*i*-Pr)$_4$ ratio was 1:3 (Table 3, entries 2–6). We also found that this reaction was strongly influenced by the solvent. Low enantioselectivities were found when CH_2Cl_2 and THF were used as the reaction solvent (Table 3, entries 7 and 8). When the amount of ligand was increased from 10% to 20% in increments of 5%, the ee values improved slightly (Table 3, entries 9 and 10), but no significant changes in ee values were observed when the temperature of the reaction was decreased from room temperature to 0 °C (Table 3, entry 11).

Table 2. Addition of phenylacetylene to benzaldehyde catalyzed by **8**.[a, b]

Entry	Method	Ligand [mol %]	$ZnEt_2$ and phenylacetylene [equivs.]	**3/4**[c]
1	**B**	**8a** (20%)	3	93/7
2	**C**	**8a** (20%)	3	> 99/1
3	**C**	**8a** (20%)	2	94/6
4	**C**	**8a** (20%)	1	93/7
5	**C**	**8b** (20%)	3	99/1
6	**C**	**8a** (10%)	3	99/1
7	**C**	**8a** (5%)	3	99/1

[a] 20 mol% **8** was used and the ratio **8**:Ti(O-*i*-Pr)$_4$ = 1:3.
[b] Toluene was solvent and Ti(O-*i*-Pr)$_4$ was freshly distilled.
[c] The ratio of **3/4** was measured by a calibrated HPLC method.

In the sulfonamide alcohol-titanium complex, the sulfonyl oxygen atom of the sulfonamide group is also chelated to metal center.[17] We wondered whether changing the sulfonamide group in the ligand would affect the outcome of the reaction. Hence, we synthesized two additional ligands, **11a** and **11b**, from L-phenylalanine methyl ester (Scheme 5) which differ from **8a** and **8b** in that they are methanesulfonamides.

When **11a** and **11b** were employed in method **C** as the catalyst in the asymmetric addition of phenylacetylene to benzaldehyde (Scheme 6 and Table 4), they catalyzed the reaction with nearly the same ees as the *p*-toluenesulfonamide catalysts, **8a** and **8b**, but the reaction yields differed. In an effort to explore this, we varied the ratio of ligand, **11a**, and Ti(O-*i*-Pr)$_4$ (entries 1–5). The best results were obtained when the **11a**/Ti(O-*i*-Pr)$_4$ ratio was 1/2. Under these conditions, the ee purity of **3** was 92% and the ratio of **3/4** was 92/8 (entry 2). Although **11b** and **8b** are very similar in structure, they gave very different enantioselectivities (entries 5–10). When 10 mol % of **11b** was used, the ee of **3** was 51% and ratio of **3/4** was 80/20 (entry 7). It is clear from these experimental results that the sulfonamide not only has an important influence on ee (**11b** *vs.* **8b**, 51% *vs.* 10%), but also influences the product ratio of **3/4** (**11a** *vs.* **8a**, 92/8 *vs.* > 99/1).

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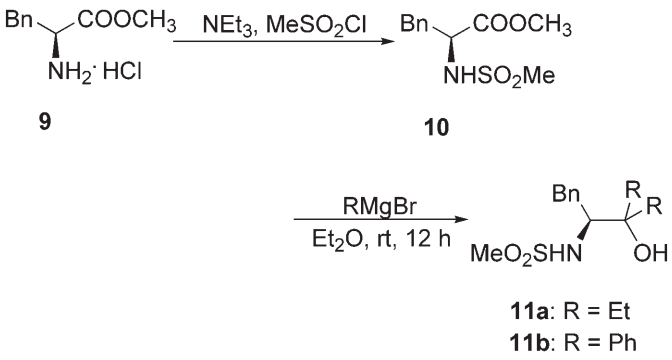
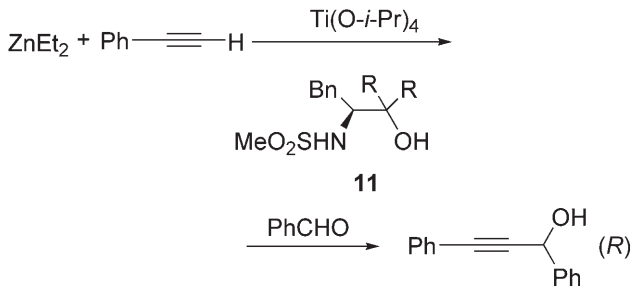
Table 3. Asymmetric addition phenylacetylene to benzaldehyde by method **C** and using **8a** and **8b** as ligands.[a]

Entry	Ligand [mol %]	Ligand/Ti(O-*i*-Pr)$_4$[b]	Solvent	Temp.	ee [%][c, d]
1	**8b** (10%)	1/3	toluene	rt	10
2	**8a** (10%)	1/3	toluene	rt	90
3	**8a** (10%)	1/1	toluene	rt	11
4	**8a** (10%)	1/2	toluene	rt	88
5	**8a** (10%)	1/4	toluene	rt	85
6	**8a** (10%)	1/5	toluene	rt	78
7	**8a** (10%)	1/3	CH_2Cl_2	rt	4
8	**8a** (10%)	1/3	THF	rt	6
9	**8a** (15%)	1/3	toluene	rt	93
10	**8a** (20%)	1/3	toluene	rt	95
11	**8a** (20%)	1/3	toluene	0 °C	95

[a] Phenylacetylene:Et_2Zn:benzaldehyde = 3:3:1.
[b] Ti(O-*i*-Pr)$_4$ was freshly distilled.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column according to the literature method.[6]
[d] The absolute configuration of the product is *R*.



Scheme 5. Preparation of methanesulfonylamino alcohol.



Scheme 6. Asymmetric addition of phenylacetylene to benzaldehyde catalyzed by **11**.

Ligand **8a** was chosen to be the best overall chiral ligand to facilitate this alkynyl addition reaction. Method **C**, employing 20 mol % of **8a**, was used to prepare a

Table 4. Asymmetric addition phenylacetylene to benzaldehyde using **11a** and **11b** as ligands.[a]

Entry	Ligand	Ligand/Ti(O-*i*-Pr)$_4$	**3/4**	ee [%][b]
1	**11a**	1/1	95/5	37
2	**11a**	1/2	92/8	92
3	**11a**	1/3	85/15	92
4	**11a**	1/4	79/21	90
5	**11a**	1/5	80/20	88
6	**11b**	1/1	95/5	3
7	**11b**	1/2	80/20	51
8	**11b**	1/3	80/20	40
9	**11b**	1/4	80/20	29
10	**11b**	1/5	80/20	14

[a] In all entries, solvent is toluene, phenylacetylene: Et_2Zn:benzaldehyde = 3:3:1, ligand is 10 mol % and Ti(O-*i*-Pr)$_4$ was freshly distilled.
[b] The absolute configuration of the product is *R*.

number of enantioselective addition products from phenylacetylene and aldehydes. When aromatic aldehydes were used, products were obtained with high enantioselectivity (up to 98% ee). The use of aliphatic aldehydes resulted in lower but acceptable selectivity (Table 5).

A large body of work describing the non-linear effects of amino alcohol-based catalysts for the asymmetric addition of alkyl groups to aldehydes exists.[18] Their catalytic activity has been attributed to the monomer-dimer equilibrium of the catalyst. In contrast, reactions employing titanium tetraisopropoxide and various ligands such as BINOL, TADDOL and sulfonamides show a linear relationship between catalyst ee and product ee. Although the titanium-based catalysts are believed to be monomeric throughout the catalytic cycle, the alkoxide group maybe exchanged to give a better catalyst during the process.[20] For example, if an alkoxide was added to a

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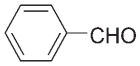
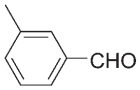
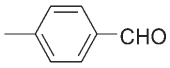
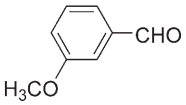
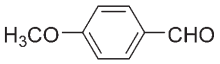
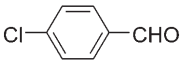
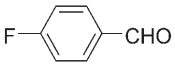
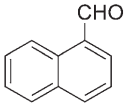
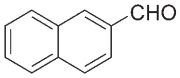
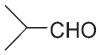
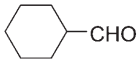
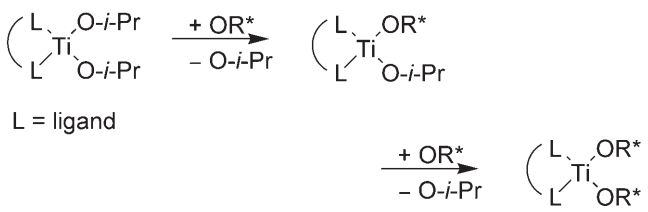
Table 5. Asymmetric addition of phenylacetylene to aldehydes promoted by ligand **8a**.[a, b,c]

Entry	Aldehydes	Time [h]	Isolated yield [%]	ee [%][d]
1		12	92	95
2		12	89	92
3		12	90	93
4		12	88	90
5		14	91	92
6		12	80	98
7		12	87	93
8		18	70	90
9		18	71	95
10		12	86	81
11		12	81	70

[a] In all of the entries: Et_2Zn:phenylacetylene:aldehyde: Ti(O-*i*-Pr)$_4$:**8a** = 3:3:1:0.6:0.2.
[b] All the reactions were processed under argon and at room temperature.
[c] Ti(O-*i*-Pr)$_4$was freshly distilled before use.
[d] The ee values were determined by chiral HPLC with a Chiracel OD column according to the literature method.[6]

titanium isopropoxide-based catalyst, it could exchange with the isopropoxide and form a new catalyst (Scheme 7). The resulting new complex often has different catalytic behavior that sometimes results in a better outcome. Over the past decade, reports of stoichiometric or sub-stoichiometric quantities of achiral additives to these systems which result in a significant increase in the rate and/or the enantioselectivity of organic transformations have sporadically appeared in the literature.[19]



Scheme 7. The alkoxide exchange in titanium-based catalysts.

When phenylacetylene was added to benzaldehyde under the above optimized conditions using 5 mol % of **8a** as the catalyst the product had an ee of 81% (Table 6, entry 1). In an effort to enhance the efficiency of the ligand, we tried adding alcohols to the reaction. When 10 mol % MeOH and EtOH were added, the ee rose slightly (entries 2 and 7). MeOH had the most significant effect and could boost the product's ee to 92% without decreasing the overall yield. We varied the ratio of **8a**/MeOH from 1/1, 1/2 to 1/5 and found that the ee was highest when the ratio was 1/2 (entries 2–6). Addition of other achiral molecules including *tert*-BuOH, phenol, naphthol and DMPEG all decreased the catalyst's enantioselectivity (entries 8–12). Chiral additives such as (*R*)-BINOL and (*S*)-BINOL (5 mol %) also resulted in decreased selectivity (entry 13). It is interesting that when (*R*)-BINOL was added, the absolute configuration of product changed from *R* to *S* (Entry 14).

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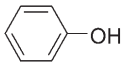
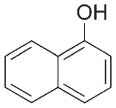
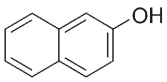
Table 6. Use of additives in the **8a**-catalyzed asymmetric addition of phenylacetylene to benzaldehyde.[a]

Entry	Additive	Ligand/additive	ee [%][b]
1	none	–	81
2	MeOH	1/1	87
3	MeOH	1/2	92
4	MeOH	1/3	85
5	MeOH	1/4	72
6	MeOH	1/5	60
7	EtOH	1/2	85
8	*t*-BuOH	1/2	79
9	DMPEG	1/2	77
10		1/2	74
11		1/2	69
12		1/2	63
13	(*S*)-BINOL	1/1	68
14	(*R*)-BINOL	1/1	37

[a] In all of the entries: 5 mol % **8a** was used; Et_2Zn:phenylacetylene: benzaldehyde:$Ti(O\text{-}i\text{-}Pr)_4 = 3:3:1:0.6$.

[b] The absolute configuration of the product is *R* except for entry 14.

The enantioselective addition of phenylacetylene to a variety of aldehydes (Table 7) was investigated using 5 mol % of compound **8a** as the chiral ligand with 10 mol % of MeOH as additive. In nearly all cases enantioselectivities > 90% could be obtained for aromatic aldehydes. Only *m*-anisaldehyde and α-naphthaldehyde gave lower ee, 80% and 86%, respectively. Aliphatic aldehydes, however, gave lower ee than the aromatic aldehydes, with phenylacetaldehyde showing the highest ee.

Conclusion

It is generally accepted that when the chiral ligands of BINOL, TADDOL, or sulfonamide alcohols are chelated with titanium tetroisopropoxide, they function equally well as catalysts for reactions such as, e.g., the addition of alkynyl groups to aldehydes.[11] In this paper, we report that when these different ligands are combined to prepare a titanium-based catalyst with $ZnEt_2$ under similar conditions and at room temperature, the main reaction product between the alkyne and aldehyde differs. BINOL-Ti and TADDOL-Ti prefer to add the ethyl group of $ZnEt_2$ to the aldehyde, whereas the sulfonamide alcohol-Ti complex favors the addition of alkyne to the substrate. We found that the Lewis acidity of the ligand correlated well with chemical selectivity: the stronger the Lewis acid, the smaller the percentage of alkyne addition product formed.

We have prepared a series of β-sulfonamide alcohols from L-phenylalanine in three steps and in good yield to act as ligands in this reaction. Among the ligands prepared compound **8a** exhibited the best catalytic activity in the enantioselective addition of phenylacetylene to aldehydes under very mild conditions, resulting in high ee and good yield. Furthermore, we found that a small amount of MeOH used as additive in the reaction enhanced the efficiency of the catalyst.

Experimental Section

General Remarks

All manipulations were carried out under an argon atmosphere using dried and degassed solvents. Sulfonylamino alcohols **8a** and **8b** were synthesized according to literature procedures.[16]

(*S*)-2-(*p*-Toluenesulfonylamino)-1,1-diethyl-3-phenyl-1-propanol [(*S*)-8a]: White needles; yield: 62%; mp 95–96 °C; $[\alpha]_D^{20}$: −39 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 0.84–0.95 (m, 6H, CH_3), 1.43–1.75 (m, 4H, CH_2Me), 2.01 (s, 1H, OH), 2.37 (s, 3H, $PhCH_3$), 2.48 (dd, $^3J_{H,H}$ = 9.2 Hz, $^2J_{H,H}$ = 14.2 Hz, 1H, $PhCH_AH_B$), 2.94 (dd, $^3J_{H,H}$ = 6.2 Hz, $^2J_{H,H}$ = 14.2 Hz, 1H, $PhCH_AH_B$), 4.65 (m, 1H, CHN), 4.75 (s, 1H, NH), 6.93–7.40 (m, 9H, 2Ph); IR (KBr): ν = 3512, 3287, 3066, 3028, 2969, 2882, 1648, 1599, 1457, 1321, 1152, 1086, 960, 908, 812, 736, 698 cm^{-1}; MS (ESI): *m/z* = 360 $[M-H]^-$.

(*S*)-2-(*p*-Toluenesulfonylamino)-1,1,3-triphenyl-1-propanol [(*S*)-8b]: White needles; yield: 67%; mp 122–123 °C; $[\alpha]_D^{20}$: +105 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 2.37 (s, 3H, CH_3), 2.53 (s, 1H, OH), 2.86 (dd, $^3J_{H,H}$ = 6.0 Hz, $^2J_{H,H}$ = 14.2 Hz, 1H, $PhCH_AH_B$), 3.27 (dd, $^3J_{H,H}$ = 3.6 Hz, $^2J_{H,H}$ = 14.2 Hz, 1H, $PhCH_AH_B$), 4.69 (m, 1H, CHN), 4.86 (d, $^3J_{H,H}$ = 8.2 Hz, 1H, NH), 6.96–7.52 (m, 19H, 4Ph); IR (KBr): ν = 3528, 3303, 3066, 3028, 2926, 1660, 1598, 1493, 1448, 1324, 1153, 1087, 968, 908, 811, 740, 700 cm^{-1}; MS (ESI): *m/z* = 456$[M-H]^-$.

(*S*)-Methyl 3-Phenyl-2-(methanesulfonamino)-propanoate (10)

L-Phenylalanine methyl ester hydrochloride (**9**; 2.16 g, 10 mmol) was suspended in 25 mL dry diethyl ether and stirred. After the system was cooled to 0 °C, NEt_3 (4.2 mL, 30 mmol) was added. Methanesulfonyl chloride (0.93 mL, 12 mmol) was dissolved in 10 mL dry diethyl ether and added to the system dropwise during 30 minutes. The system was warmed to room temperature and stirred overnight. After the reaction was complete as checked by TLC, the mixture was cooled to 0 °C and washed with 10 mL 5% aqueous NaOH three times and with brine two times, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexane) to give the product; yield: 85%; white needles; mp 48–50 °C; $[\alpha]_D^{20}$: −25 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 2.55 (s, 3H, CH_3), 2.95 (dd, $^3J_{H,H}$ = 4.8 Hz,

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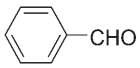
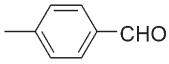
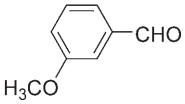
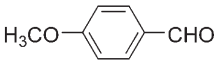
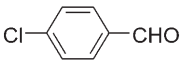
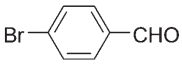
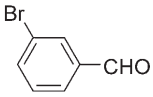
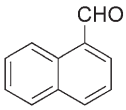
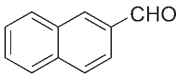
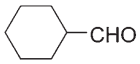
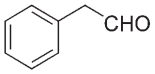
Table 7. **8a**-catalyzed asymmetric addition of phenylacetylene to aldehydes using MeOH as additive.[a, b,c]

Entry	Aldehyde	Time [h]	Isolated yield [%]	ee [%][d]
1		12	95	92
2		12	92	95
3		12	89	80
4		12	91	95
5		12	83	94
6		12	83	92
7		12	86	90
8[e]		18	62	86
9[e]		18	67	97
10		15	89	76
11		15	91	68
12		15	83	99

[a] In all of the entries: 5 mol % **8a** and 10 mol % MeOH were used; Et_2Zn:phenylacetylene:aldehyde:Ti(O-*i*-Pr)$_4$:**8a** = 3:3:1:0.6:0.05.
[b] All the reactions were processed under argon and at room temperature.
[c] Ti(O-*i*-Pr)$_4$ was freshly distilled before use.
[d] The ee values were determined by chiral HPLC with a Chiracel OD column according to the literature method.[6]
[e] We found a significant amount of ethyl-added product when naphthaldehyde was the substrate.

$^2J_{H,H}$ = 12.8 Hz, 1H, $PhCH_AH_B$), 3.12 (dd, $^3J_{H,H}$ = 4.8 Hz, $^2J_{H,H}$ = 12.8 Hz, 1H, $PhCH_AH_B$), 3.69 (s, 3H, CH_3), 4.32 (m, 1H, CH), 5.73 (d, 1H, NH), 7.18–7.28 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 171.8, 135.7, 129.3, 129.1, 126.9, 57.1, 52.3, 40.9, 38.8; MS (FAB): *m/z* = 258 $[M+H]^+$; anal. calcd. for C11H14NO4S: C 51.35, H 5.88; found: C 51.39, H, 5.76.

(*S*)-2-(Methanesulfonylamino)-1,1-diethyl-3-phenyl-1-propanol [(*S*)-11a]:

Ester **10** (1.1 g, 4.3 mmol) was dissolved in 20 mL dry diethyl ether and stirred at 0 °C. Then 4 equivs. of EtMgBr were added to the mixture dropwise and the system was warmed to room temperature. After the reaction was complete as checked by TLC, the mixture was cooled to 0 °C and quenched by saturated aqueous NH_4Cl. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexane) to give the product; yield: 86%; white crystals; mp 101–103 °C; $[\alpha]_D^{20}$: −73 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.95–1.0 (m, 6H, $2CH_3$), 1.54–1.79 (m, 4H, $2CH_2$), 1.90 (s, 3H, CH_3), 1.95 (brs, 1H, OH), 2.55 (dd, $^3J_{H,H}$ = 12 Hz, $^2J_{H,H}$ = 14 Hz, 1H, $PhCH_AH_B$), 3.05 (dd, $^3J_{H,H}$ = 3.2 Hz, $^2J_{H,H}$ = 14 Hz, 1H, $PhCH_AH_B$), 3.65 (m, 1H, CH), 4.71 (d, 1H, NH), 7.22–7.35 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 139.3, 130.0, 128.8, 127.0, 76.4, 62.2, 40.9, 36.4, 27.9, 7.6; HR-MS (ESI): *m/z* = 303.1743, calcd. for $[M+NH_4]^+$: 303.1737.

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(*S*)-2-(Methanesulfonylamino)-1,1,3-triphenyl-1-propanol [(S)-11b]:

Ester **10** (1.1 g, 4.3 mmol) was dissolved in 20 mL dry diethyl ether and stirred at 0 °C. Then 4 equivs. of PhMgBr were added into the mixture dropwise and the system was warmed to room temperature. After the reaction was complete as checked by TLC, the mixture was cooled to 0 °C and quenched by saturated aqueous NH_4Cl. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexane) to give the product; yield: 78%; white crystals; mp 184–186 °C; $[\alpha]_D^{20}$: +106 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 1.81$ (s, 3H, CH_3), 2.06 (brs, 1H, OH), 2.80 (dd, $^3J_{H,H} = 10.4$ Hz, $^2J_{H,H} = 14.4$ Hz, 1H, $PhCH_AH_B$), 2.98 (dd, $^3J_{H,H} = 2.4$ Hz, $^2J_{H,H} = 14.4$ Hz, 1H, $PhCH_AH_B$), 4.90 (m, 1H, CH), 5.75 (d, 1H, NH), 7.15–7.42 (m, 10H, 2Ph), 7.72–7.79 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 146.7$, 140.2, 130.8, 129.1, 128.7, 127.6, 127.5, 127.0, 81.8, 64.4, 42.0, 38.9; HR-MS (ESI): $m/z = 399.1741$; calcd. for $[M+NH_4]^+$: 399.1737.

General Procedures for the Addition of Phenylacetylene to Aldehydes

Method A: Under argon, a solution of Et_2Zn (1.0 M in toluene, 1.5 mL) and phenylacetylene (165 μL, 1.5 mmol) was combined in 2 mL toluene and refluxed for 5 hours. Then, the system was cooled to room temperature, the ligand (0.05 mmol) and Ti(O-*i*-Pr)$_4$ (41 μL, 0.15 mmol) were added. After stirred had been continued for 0.5 h, the aldehyde (0.5 mmol) was added and stirred at room temperature. After the reaction was complete as checked by TLC, the mixture was cooled to 0 °C and quenched by 5% aqueous HCl. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 12.5% EtOAc in hexane) to give the product.

Method B: Under argon, the ligand (0.05 mmol) and Ti(O-*i*-Pr)$_4$ (41 μL, 0.15 mmol) were mixed in dry toluene at room temperature. Then, a solution of Et_2Zn (1.0 M in toluene, 1.5 mL), was added. After the mixture had been stirred at room temperature for 1 h, phenylacetylene (165 μL, 1.5 mmol) and aldehyde (0.5 mmol) were added together and stirred at room temperature. After the reaction was complete as checked by TLC, the mixture was quenched and purified by the same procedure as method A.

Method C: Under argon, the ligand and Ti(O-*i*-Pr)$_4$ were mixed in dry toluene at room temperature. Then, a solution of Et_2Zn was added. After the mixture had been stirred at room temperature for 1 h, phenylacetylene was added and stirred for another 1 hour. The orange solution was cooled to 0 °C and treated with aldehyde, then, the resultant mixture was allowed to warm up to room temperature. After the reaction was complete as checked by TLC, the mixture was quenched and purified by the same procedure as for method A.

General Procedure for the Addition of Phenylacetylene to Aldehydes using MeOH as Additive

Under argon, the ligand **8b** (9 mg, 0.025 mmol) and Ti(O-*i*-Pr)$_4$ (20.5 μL, 0.075 mmol) were mixed in dry toluene at room temperature. Then, a solution of Et_2Zn (1.0 M in toluene, 1.5 mL), was added. After the mixture had been stirred at room temperature for 1 h, phenylacetylene (165 μL, 1.5 mmol) was added and stirred for 30 min. Then, MeOH (2 μL, 0.05 mmol) was added to the system and stirred for another 30 min. The rest of the procedure was the same as described in method C.

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