Asymmetric Additions

Highly Enantioselective Addition of Phenylacetylene to Aldehydes Catalyzed by a β-Sulfonamide Alcohol–Titanium Complex**

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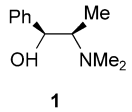
The enantioselective formation of C–C bonds is an area of intense research.[1,2] The asymmetric addition of alkynyl reagents to aldehydes is very useful for the synthesis of chiral secondary propargyl alcohols, which are important building blocks for many chiral organic compounds.[3] Several studies into the alkynylation of aldehydes with amino alcohol ligands have led to methods that give moderate to good yields and enantioselectivities.[4] Carreira and co-workers reported the addition of terminal acetylenes to aliphatic aldehydes in the presence of stoichiometric or catalytic amounts of amino alcohol **1** to give the desired products in high yields and enantioselectivities. However, this method was not suitable for the addition reaction to aromatic aldehydes because of significant competition from the Cannizzaro reaction.[5]



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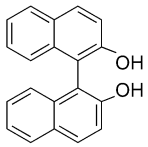

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Recently, Chan and co-workers reported that binol (**2**) can catalyze the addition of alkynyl zinc reagents to aromatic aldehydes with high *ee* values. However, the reaction also requires 1 equivalent of a sulfonamide ligand and must be run at 0 °C for 1–2 days.[6] Pu and co-workers reported that a

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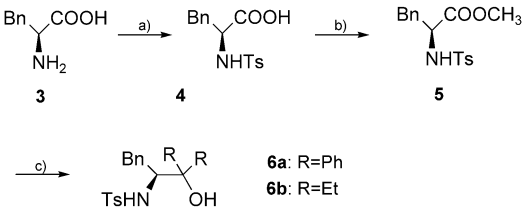
binol–Ti complex can also catalyze this reaction, but this method requires a separate step for the preparation of the alkynyl zinc reagent at high temperatures for 5 h.[7] Thus there is a growing need to find an inexpensive and novel catalyst for the asymmetric addition of terminal acetylenes to aromatic aldehydes; the reaction should be fast, occur in a single step under mild and convenient conditions, and should also lead to has *ee* values.

The N-H group of sulfonamides is acidic owing to the highly electron-withdrawing nature of the sulfonyl group. Therefore, unlike traditional metal amides ($M\text{-}NR_2$), the sulfonamide nitrogen atom is a poor electron donor and sulfonamide–Ti complexes are Lewis acids.[8] Aminoalcohols derived from natural amino acids are among the best and most economical ligands available.[9] We therefore decided to prepare a few β-sulfonamide alcohols **6** (Scheme 1). As a result of the acidic N-H and O-H groups, a titanium complex is readily formed when combined with $Ti(OiPr)_4$ under basic conditions.[10] These complexes behave similarly to binol–Ti complexes, and we therefore applied them in the enantioselective addition of phenylacetylene to aldehydes.

Three simple steps were required to prepare **6a** and **6b** from L-phenylalanine in overall yields of 67% and 62%, respectively (Scheme 1). The two ligands were initially tested

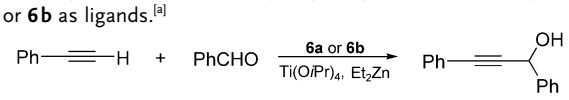


Scheme 1. Preparation of sulfonamide from L-phenylalanine. a) NaOH (2 equiv), H_2O, TsCl (1 equiv), Et_2O, room temperature, 24 h; b) $SOCl_2$ (1.2 equiv), MeOH, −30°C, 30 min; then reflux, 2 h; c) RMgBr (5 equiv), THF, room temperature, 24 h. Ts = *p*-toluenesulfonyl.

in the asymmetric addition of phenylacetylene to benzaldehyde in the presence of diethylzinc (Table 1). Interestingly, **6a**, which has the bulkier, less-flexible phenyl substituents at the hydroxy-bearing carbon atom, resulted in a lower enantioselectivity (Table 1, entry 1) than **6b**, which has the more-flexible ethyl substituents (Table 1, entry 2). We varied the amount of $Ti(OiPr)_4$ and found that the best *ee* are obtained when the **6b**/$Ti(OiPr)_4$ ratio is 1:3 (Table 1, entries 2–6). We also found that this reaction was strongly influenced by the solvent: Low enantioselectivities were found in CH_2Cl_2 and THF (Table 1, entries 7 and 8). When the amount of ligand increased from 10% to 15 and 20%, the *ee* values improved slightly (Table 1, entries 9 and 10). No significant changes in *ee* values were observed when the temperature of the reaction was decreased from room temperature to 0°C (Table 1, entry 11).

Under these optimized reaction conditions, ligand **6b** was employed to induce the enantioselective addition of phenylacetylene to a number of aromatic aldehydes,[11] all of which gave rise to products with high enantioselectivity (up to 98% *ee*; Table 2).

Table 1: Asymmetric addition of phenylacetylene to benzaldehyde with **6a** or **6b** as ligands.[a]



Entry	Ligand	[mol%]	Ligand/$Ti(OiPr)_4$[b]	Solvent	*T*	*ee* [%][c]
1	**6a**	10	1:3	toluene	RT	10
2	**6b**	10	1:3	toluene	RT	90
3	**6b**	10	1:1	toluene	RT	11
4	**6b**	10	1:2	toluene	RT	88
5	**6b**	10	1:4	toluene	RT	85
6	**6b**	10	1:5	toluene	RT	78
7	**6b**	10	1:3	CH_2Cl_2	RT	4
8	**6b**	10	1:3	THF	RT	6
9	**6b**	15	1:3	toluene	RT	93
10	**6b**	20	1:3	toluene	RT	95
11	**6b**	20	1:3	toluene	0°C	95

[a] Phenylacetylene/Et_2Zn/benzaldehyde = 3:3:1. [b] $Ti(OiPr)_4$ was freshly distilled. [c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OJ-H column.

Table 2: Asymmetric addition phenylacetylene to aromatic aldehydes promoted by ligand **6b**.[a]

Entry	Aldehyde	*t* [h]	Yield [%]	*ee* [%][b]
1	benzaldehyde	12	92	95
2	3-tolualdehyde	12	89	92
3	4-tolualdehyde	12	90	93
4	3-anisaldehyde	12	88	90
5	4-anisaldehyde	14	91	92
6	4-chlorobenzaldehyde	12	80	98
7	4-fluorohenzaldehyde	12	87	93
8	α-naphthaldehyde	18	70	90
9	β-naphthaldehyde	18	71	95

[a] Et_2Zn/phenylacetylene/aldehyde/$Ti(OiPr)_4$/**6b** = 3:3:1:0.6:0.2. All the reactions were processed under argon and at room temperature. $Ti(OiPr)_4$ was fresh distilled before use. [d] The *ee* values were determined by chiral HPLC on a Chiracel OJ-H column.

In conclusion, we successfully prepared two β-sulfonamide alcohol ligands from natural L-phenylalanine in three steps in good yields. Ligand **6b** exhibits excellent catalytic activity in the enantioselective addition of phenylacetylene to aromatic aldehydes under very mild conditions.

Experimental Section

All manipulations were carried out under an argon atmosphere in dried and degassed solvent. β-Sulfonamide alcohols **6a** and **6b** were synthesized according to literature procedures.[12]

(*S*)-**6a**. White needles (67% yield); m.p. 122–123°C; $[\alpha]_D^{20} = +105$ ($c = 0.121$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 3528, 3303, 3066, 3028, 2926, 1660, 1598, 1493, 1448, 1324, 1153, 1087, 968, 908, 811, 740, 700\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 2.37$ (s, 3H; CH_3), 2.53 (s, 1H; OH), 2.86 (dd, ^3J(H-H) = 6.0, ^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 ppm (m, 19H; 4 × Ph-H); MS (ESI): *m/z*: 456 $[M-H]^-$.

(*S*)-**6b**. White needles (62% yield); m.p. 95–96°C; $[\alpha]_D^{20} = -39$ ($c = 0.102$ in $CHCl_3$); IR(KBr): $\tilde{\nu} = 3512, 3287, 3066, 3028, 2969, 2882, 1648, 1599, 1457, 1321, 1152, 1086, 960, 908, 812, 736, 698\ cm^{-1}$; ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 0.84$–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$_A$$H_B$), 4.65 (m, 1H; CHN), 4.75 (s, 1H; NH), 6.93–7.40 ppm (m, 9H; 2 × Ph-H); MS (ESI): *m*/*z*: 360 $[M-H]^-$.

General addition procedure: Under argon, the ligand **6b** (18 mg, 0.05 mmol) and Ti(O*i*Pr)$_4$ (41.2 μL, 0.15 mmol) were mixed in dry toluene at room temperature. A solution of Et_2Zn (1.0 M in toluene, 0.75 mL) was then added. After the mixture was stirred at the room temperature for 2 h, phenylacetylene (82.4 μL, 0.75 mmol) was added and the stirring continued for 1 h. The orange solution was cooled to 0 °C and treated with aldehyde (0.25 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 12–18 h. After the reaction was complete (monitoring with TLC), it was cooled to 0 °C and quenched with aqueous HCl (5%). The mixture was extracted with diethyl 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.

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