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Highly Enantioselective Phenylacetylene Addition to Aromatic Ketones Catalyzed by Cinchona Alkaloid−Aluminum Complexes

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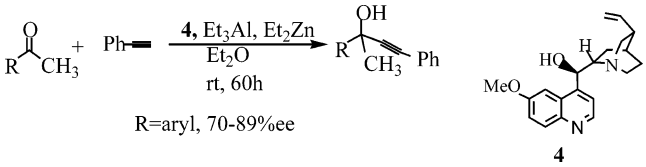

The catalytic asymmetric addition of phenylacetylene to aromatic ketones is reported. The catalyst, generated from commercially available Cinchona alkaloids and industrially available triethylaluminum, gives the expected tertiary alcohols with good enantiomeric excess (70−89%) and yields (60−83%). No previous case has been reported successfully using triethylaluminum as a Lewis acid in the asymmetric alkynylation of carbonylic derivatives, and thus we provide a new method to obtain optically active tertiary propargyl alcohols.

Optically active propargyl alcohols are important precursors for the synthesis of many organic compounds. One of the simplest ways to synthesize these alcohols is the enantioselective addition of alkynylzinc reagents to carbonylic derivatives. The asymmetric alkynylzinc addition to aldehydes has been studied extensively.[1,2] In sharp contrast, the use of ketones as alkyl and aryl group acceptors under similar conditions has proven to be much more challenging. This discrepancy is due to the reduced propensity of ketones to coordinate to Lewis acids, relative to aldehydes. Although Jiang[3] has reported the addition of alkynes to α-keto esters with good yields and enantioselectivities, the ketones were activated by electron-withdrawing groups. Only very recently have the first examples of chiral ligands that enable the addition of alkynylzinc reagents to unactivated ketones been described independently and simultaneously. P. G. Cozzi[4] reported a Zn(salen) bifunctional catalyst, **1** (20 mol %), which promotes alkynylation of ketones with moderate yields and enantioselectivities. However, the catalytic system is substantially less effective on aromatic substrates (ee values ranged from 53 to 70% and yields ranged from 45 to 81% for aryl methyl ketones). In the same year, Chan[5] and co-workers described the alkynylzinc addition to ketones in the presence of chiral camphorsulfonamide ligand **2** using $Cu(OTf)_2$ as a promoter with high enantioselectivities and yields. Katsuki[6] demonstrated the addition of alkynylzinc reagents to aliphatic ketones with chiral salen catalysts to give a maximum ee value of 91%. In addition, P. G. Cozzi[7] developed a practical method for the synthesis of chiral tertiary propargyl alcohols in the presence of titanium phenylacetylide (obtained by the transmetalation of lithium alkynyl derivatives with $ClTi(O^iPr)_3$) and (*R*)-BINOL (25 mol %). The reaction was performed at −15 or −30 °C with up to 90% ee values. At the same time, we[8] found that (*S*)-BINOL (20 mol %) was an efficient catalyst for asymmetric alkynylation of aromatic ketones when the ratio of BINOL to $Ti(O^iPr)_4$ was 1.0, and good to excellent enantioselectivities were achieved.

To the best of our knowledge, the reaction of the phenylacetylene addition to carbonylic derivatives has so far only been catalyzed by Lewis acids based on zinc,[1e,2d,4,6] copper,[5] and titanium.[2a−c,7,8] The reaction path in the aluminum-catalyzed reactions has not been established. In view of the importance of the tertiary propargyl alcohols as precursors of many important pharmaceuticals, the development of an efficient catalyst that is inexpensive and commercially available is not only of interest to the academic world but also of substantial interest to industrial scientists. Singh[9] examined Cinchona alkaloids for alkynylzinc addition to aldehydes, and it was found that cinchonidine **5** (40 mol %) catalyzed the reaction with 62−85% ee in the presence of $Ti(O^iPr)_4$. Herein, we report the first example of the asymmetric

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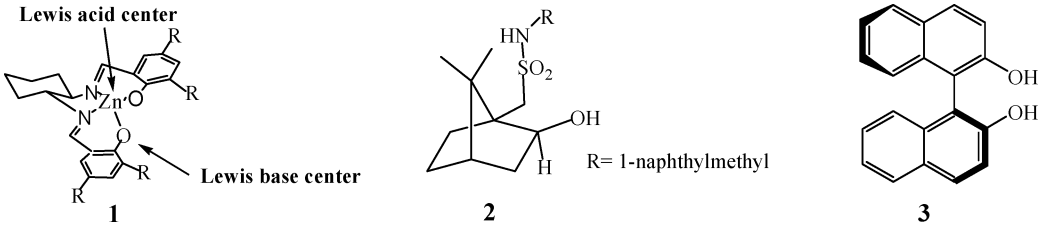


FIGURE 1. Chiral catalysts evaluated in asymmetric alkynylation of ketones.

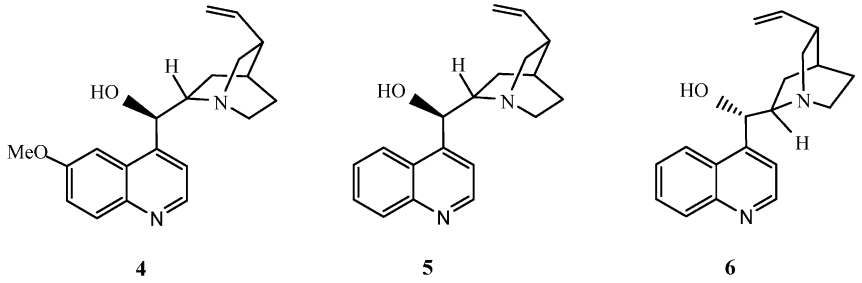


FIGURE 2. Three kinds of Cinchona alkaloids

TABLE 1. Effect of Ligands and Lewis Acids

entry	ligand (L*)	condition[a–d]	ee (%)[e]	yield (%)[f]
1	**4**	$Ti(O^iPr)_4$	40	68
2	**4**	$Al(O^iPr)_3$	76	59
3	**4**	$Al(O^iPr)_3$[g]	71	70
4	**4**	$Al(O^iPr)_3$[h]	55	82
5	**4**	Et_3Al	80	70
6	**4**	$Cu(OTf)_2$	7	53
7	**4**		5	78
8	**5**	$Ti(O^iPr)_4$		
9	**5**	$Al(O^iPr)_3$	73	55
10	**5**	Et_3Al	62	61
11	**6**	$Ti(O^iPr)_4$	27	60
12	**6**	$Al(O^iPr)_3$	76	57
13	**6**	Et_3Al	55	62

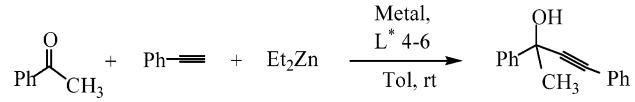
[a] Molar ratio of $PhCOCH_3$:PhCCH:Et_2Zn:$Al(O^iPr)_3$:L* = 1:2:2:0.5:0.5. [b] Molar ratio of $PhCOCH_3$:PhCCH:Et_2Zn:$Al(O^iPr)_3$:L* = 1:2:2.4:0.8:1. [c] Molar ratio of $PhCOCH_3$:PhCCH:Et_2Zn:Et_3Al:L* = 1:2:2:0.4:0.8. [d] Molar ratio of $PhCOCH_3$:PhCCH:Et_2Zn:$Cu(OTf)_2$:L* = 1:2:2:0.5:0.5. [e] % ee was determined by HPLC on a chiralcel OD column. [f] Yield of isolated product. [g] Performed with 3 equiv of Et_2Zn. [h] Performed with 4 equiv of Et_2Zn.

alkynylation of ketones employing Cinchona alkaloids as ligands and triethylaluminum as a Lewis acid. Cinchona alkaloids are commercially available, and triethylaluminum reagent is economically prepared in industrial scale from aluminum hydride and olefins, so it may be applied in technochemistry.

Results and Discussion

During our initial studies (see Table 1), cinchonidine **5** was applied in the reaction of alkynylzinc reagents to acetophenone in the presence of $Ti(O^iPr)_4$ according to Singh's method, but no desired product was observed (entry 8). Quinine **4** and cinchonine **6** were also used to promote the reaction, and they gave maximum ee values of 40 and 27%, respectively (entries 1 and 11). Unlike the reaction catalyzed by (*S*)-BINOL,[8] varying the amount of $Ti(O^iPr)_4$ did not influence the enantioselectivities. Then, we employed **4** to screen for the most efficient

SCHEME 1. Asymmetric Alkynylation of Acetophenone Catalyzed by 4–6 Using Diverse Lewis Acids



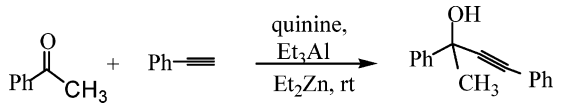
Lewis acid was in the reaction. When $Cu(OTf)_2$ and $Al(O^iPr)_3$ were used instead of $Ti(O^iPr)_4$, **4** gave 7 and 76% ee, respectively (entries 6 and 2), and poor enantioselectivity was obtained when no additional central metal was added (entry 7). In the presence of $Al(O^iPr)_3$ and **4**, we changed the amount of Et_2Zn and found that the more the Et_2Zn was used, the lower the ee value was obtained (entries 2–4). When quinine-Al catalyst was generated, 1 equiv of 2-propanol was created, and without doubt 2-propanol would consume an equivalent amount of Et_2Zn. To ensure that the reaction was complete, the amount of Et_2Zn could not be lower than a certain level. We suspected that if no 2-propanol was created when the catalyst was generated, no Et_2Zn would be consumed. Thus, the amount of Et_2Zn could be decreased to a lower degree, and the enantiomeric excess might be improved. Fortunately, our tentative plan was correct. When Et_3Al was employed, the corresponding enantiomeric excess was 80% and the yield was also improved (entry 5). On the basis of the foregoing studies, quinine was the most effective catalyst in the presence of Et_3Al as a Lewis acid (entries 5, 10, and 13). The conditions of the asymmetric alkynylation of acetophenone in the presence of quinine-Al were optimized, and the results are summarized in Table 2. The first observation is that the enantioselectivity of the reaction is not influenced by varying the amount of quinine from 80 to 100 mol % (entries 1–3). The optimum ratio of aluminum salt to quinine was 0.50 (entries 4–6). When the amount of diethylzinc was increased from 1.6 to 3 equiv, the reaction proceeded faster but the ee decreased from 81 to 62% (entries 7, 2, and 5). The reaction was strongly influenced by the solvents. Diethyl ether was the best, affording 86% ee (entry 8), while THF obviously made the reaction slug-

TABLE 2. Asymmetric Addition of Phenylacetylene to Acetophenone[a]

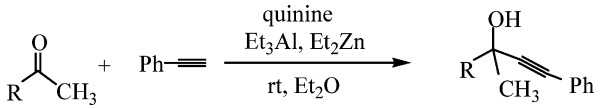
entry	ligand (mol %)	solvent	Et_3Al/quinine	Et_2Zn	ee[b] (%)	yield[c] (%)
1	50	Tol	0.5	200	65	60
2	80	Tol	0.5	200	80	70
3	100	Tol	0.5	200	80	65
4	80	Tol	1.0	300	50	89
5	80	Tol	0.5	300	62	85
6	80	Tol	0.3	300	58	77
7	80	Tol	0.5	160	81	68
8	80	Et_2O	0.5	160	86	61
9	80	CH_2Cl_2	0.5	160	72	45
10	80	Hex	0.5	160	59	60
11	80	THF	0.5	160		
12[d]	80	Et_2O	0.5	160		
13	80	Et_2O	3	0		
14[e]	80	Tol	3.75	0	3	78
15[f]	80	Tol	0.5	160	71	50

[a] All reactions, unless otherwise stated, were carried out for 60 h at room temperature. [b] Enantiomeric excess was determined by HPLC on a chiralcel OD column. [c] Yield of isolated product. [d] Reaction was performed at 0 °C. [e] Alkynyldiethylalanes were used instead of alkynylzinc. [f] ^{i}PrOH was added.

SCHEME 2. Asymmetric Addition of Phenylacetylene to Acetophenone Catalyzed by Ligand 4



SCHEME 3. Asymmetric Addition of Phenylacetylene to Ketones Promoted by Ligand 4



gish, producing no reaction (entry 11). When the reaction temperature was decreased from room temperature to 0 °C (entry 12) or only Et_3Al was added (entry 13), no desired product was observed. When we used alkynyldiethylalanes,[10] which could be simply obtained using phenylacetylene and Et_3Al, instead of alkynylzinc, only 3% ee was given (entry 14). Addition of 2-propanol as an additive was not of any help (entry 15). Under such optimized reaction conditions, quinine-Al catalyst was employed to induce the enantioselective addition of phenylacetylene to a family of aromatic ketones with 70−89% ee. The reactions of the phenylacetylene addition to aliphatic ketones and α,β-unsaturated ketones were also observed. The product that was generated from 4-methyl-2-pentanone was obtained with 47% ee and 88% yield, and the one that was generated from benzalacetone was obtained with 60% ee and 80% yield.

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TABLE 3. Asymmetric Addition of Phenylacetylene to Aromatic Ketones[a]

entry	ketones	ee[b] (%)	yield[c] (%)
1	acetophenone	86	61
2	2′-fluoroacetophenone	89	83
3	2′-naphthacetophenone	83	70
4	4′-chloroacetophenone	80	80
5	3′-methoxyacetophenone	84	75
6	3′-bromoacetophenone	82	81
7	4′-methylacetophenone	80	60
8	3′-methylacetophenone	76	65
9	4′-fluoroacetophenone	70	78

[a] All reactions were carried out for 60 h at room temperature. [b] Enantiomeric excess was determined by HPLC on a chiralcel OD column. [c] Yield of isolated product.

Conclusion

We have successfully described an efficient catalyst in the asymmetric alkynylzinc addition to unactivated aromatic ketones with 70−89% ee catalyzed by quinine, which is commercially available, inexpensive, and stable. In addition, triethylaluminum, which is industrially available, was first used as a Lewis acid in this reaction.

Experimental Section

Typical Experimental Procedure. Under argon, quinine (64.8 mg, 0.2 mmol) and a solution of Et_3Al (0.9 M in hexane, 0.112 mL) were mixed in dry diethyl ether (2.0 mL) at room temperature and stirred for 2 h. Then, Et_2Zn in toluene (1.0 M, 0.4 mL) was added. After that, phenylacetylene (44 μL, 0. 04 mmol) was then added. After the mixture was stirred at room temperature for another 1 h, the solution was cooled to 0 °C and treated with acetophenone (0.25 mmol, 29.4 μL). The resulting mixture was stirred for 60 h at room temperature. After the reaction was complete (monitoring with TLC), it was quenched with aqueous HCl (5%). Then, 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 to give the product.

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Supporting Information Available: General experimental procedures for the addition of phenylacetylene to ketones and the characterization of the propargylic alcohols, as well as ^1H and ^{13}C NMR spectra and HPLC data of the propargylic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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