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Highly Enantioselective Alkynylation of α-Keto Ester: An Efficient Method for Constructing a Chiral Tertiary Carbon Center

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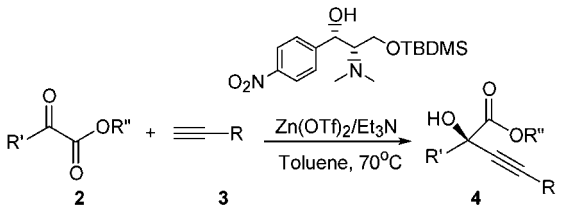
ABSTRACT



The asymmetric addition of terminal alkynes to α-keto ester was carried out using a catalytic amount of (1*S*,2*S*)-3-(*tert*-butyldimethylsilyloxyl)-2-*N*,*N*-(dimethylamino)-1-(*p*-nitrophenyl)-propane-1-ol in the presence of $Zn(OTf)_2$ to give the corresponding tertiary propargylic alcohols in high yields with up to 94% ee. *N*-Methylephedrine and $Zn(OSO_2CHF_2)_2$ were also examined in this reaction.

Optically active propargylic alcohols are important synthetic intermediates in asymmetric synthesis.[1] The methods that have been devised to prepare chiral propargylic alcohols involve either nucleophilic addition of metalated acetylenes to the carbonyl group[2] or ynone reduction.[3] Recently, great progress has been made in the stereocontrolled nucleophilic alkynylation of aldehydes to give chiral secondary propargylic alcohols in the presence of $Zn(OTf)_2$ and Et_3N.[4] Mechanistic studies of this transformation by Carreira and co-workers have demonstrated the formation of a zinc alkynylide intermediate in the course of the reaction. This observation raised the possibility of additional enantioselective alkynylation of ketones and imines. In this paper, we report that (1*S*,2*S*)-3-(*tert*-butyldimethylsilyloxyl)-2-*N*,*N*-dimethyl amino-1-(*p*-nitrophenyl)-propane-1-ol (**1**), a new inexpensive chiral amino alcohol based ligand that was developed to catalyze the asymmetric alkynylation of aldehydes,[5] can be used to catalyze the enantioselective addition of zinc alkynylide to α-ketoester to prepare tertiary α-hydroxy-*β*-ynyl ester. To date, the methods that have been reported to prepare chiral tertiary propargylic alcohols have been very limited.[6]

In preliminary studies, phenylacetylene (**3a**) underwent addition to benzoylformate (**2a**) at 50 °C for 24 h in the presence of ligand (1*S*,2*S*)-**1** (1.2 equiv), $Zn(OTf)_2$ (1.1 equiv), and Et_3N (1.1 equiv) to give a tertiary propargylic

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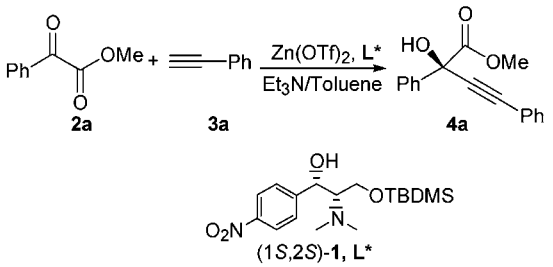
Scheme 1. Enantioselective Addition of Phenylacetylene to Benzoylformate



alcohol (**4a**) (Scheme 1) in 92% yield and 89% enantiomeric excess (entry 1, Table 1). Catalytic conditions (0.2 equiv of $Zn(OTf)_2$, 0.22 equiv of (1*S*,2*S*)-**1**, and 0.5 equiv of Et_3N in toluene at 70 °C for 1 day) gave a low yield of product (enry 2, Table 1) in 82% ee. Several conditions of the reaction (the equivalence of some additives, reaction temperature and time) were then optimized. The results are summarized in Table 1. The reaction was not improved by raising the temperature to 80 °C or by adding 0.1 equiv of DBU (very complex phenomena were observed by TLC tracing, entries 3 and 6, Table 1). Tests with other additives such as $ZnCl_2$ and LiCl resulted in no reaction (entries 4 and 5, Table 1). However, when phenylacetylene was used as solvent (PhC≡CH/keto ester = 3/1) with a slightly decreased amount of Et_3N (from 0.5 to 0.3 equiv), the reaction proceeded at 70 °C for 2 days to give product **4a** in 91% yield and 89% ee (entry 8, Table 1). Further reduction of the amount of ligand (1*S*,2*S*)-**1** was fruitless (entries 9 and 10, Table 1).

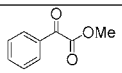
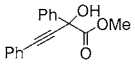
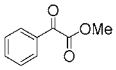
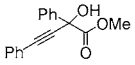
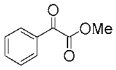
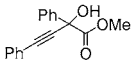
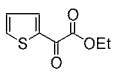
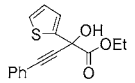
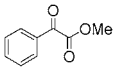
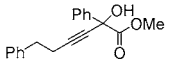
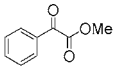
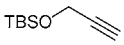
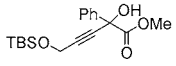
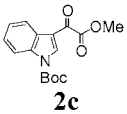
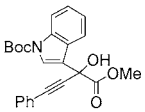
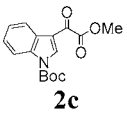
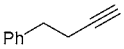
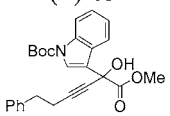
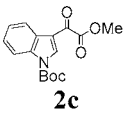
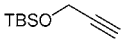
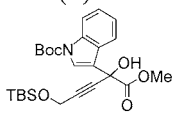
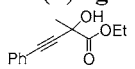
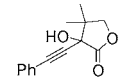
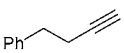
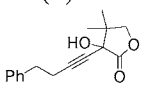
Table 1. Enantioselective Addition of PhC≡CH to Benzoylformate[a]

	L* (equiv)	Zn (equiv)	Et_3N (equiv)	time/temp (d)/(°C)	additive (equiv)	yield (%)[b]	ee[c] (%)
1	1.2	1.1	1.1	1/50		92	89
2	0.22	0.2	0.5	1/70		26	82
3	0.22	0.2	0.5	1/80		Complex	
4	0.22	0.2	0.5	1/70	$ZnCl_2$ (1)	67	13
5	0.22	0.2	0.5	1/70	LiCl (1)	<5%	
6	0.22	0.2	0.5	1/70	DBU (0.1)	complex	
7	0.22	0.2	0.5	2/70[d]		43	89
8	0.22	0.2	0.3	2/70[d]		91	89
9	0.11	0.1	0.15	3/70[d]		58	87
10	0.055	0.5	0.07	3/70[d]		22	73

[a] Reactions were carried out with the addition of (1*S*,2*S*)-**1**, $Zn(OTf)_2$, and Et_3N; the product was (+)-**4a**. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC. [d] PhC≡CH was used as solvent (PhC≡CH/keto ester = 3/1).

The reactions of various aliphatic or aromatic keto esters with several terminal alkynes under optimal conditions (entry 8 in Table 1) are summarized in Table 2. As shown, almost all of the tertiary α-hydroxy-*β*-ynyl esters were obtained with excellent enantiomeric excess (up to 94%) and high chemical yield (up to 93%). Interestingly, the heterocyclic alkyl

Table 2. Enantioselective Addition of RC≡CH to Keto Ester[a]

	keto ester	alkyne	L*	product	yield[b]/ ee[c]
1	 **2a**	 **3a**	**1**	 **(+) 4a**	91%/ 89%
2	 **2a**	 **3a**	**5**[d]	 **(-) 4a**	87%/ 88%
3	 **2a**	 **3a**	**1**[e]	 **(+) 4a**	83%/ 92%
4	 **2b**	 **3a**	**1**	 **(+) 4b**	93%/ 73%
5	 **2a**	 **3b**	**1**	 **(+) 4c**	88%/ 94%
6	 **2a**	 **3c**	**1**	 **(+) 4d**	83%/ 91%
7	 **2c**	 **3a**	**1**[f]	 **(+) 4e**	81%/ 83%
8	 **2c**	 **3b**	**1**[f]	 **(+) 4f**	76%/ 86%
9	 **2c**	 **3c**	**1**[f]	 **(+) 4g**	67%/ 81%
10	 **2d**	 **3a**	**1**	 **(-) 4h**	11%/ 92%
11	 **2e**	 **3a**	**1**	 **(+) 4I**	95%/ 93.5%
12	 **2e**	 **3b**	**1**	 **(-) 4j**	93%/ 94%

[a] Unless stated otherwise, the reactions were carried out with the addition of 0.22 equiv of (1*S*,2*S*)-**1**, 0.2 equiv of $Zn(OTf)_2$, and 0.3 equiv of Et_3N (2 mL) at 70 °C for 2 d, RC≡CH/keto ester = 3/1. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of the alcohol. [d] (−)-(1*R*,2*S*)-*N*-Methylephedrine **5** was used as ligand. [e] $Zn(OSO_2CHF_2)_2$ was used as an additive. [f] RC≡CH/keto ester = 5/1.

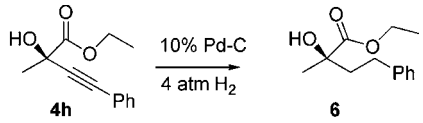
glyoxylate (**2b**, **2c**) underwent an alkynylation reaction to give the product in high yield and good enantiomeric excess. For example, the indolyl glyoxylate (**2c**) reacted with phenylacetylene (**3a**) or aliphatic acetylene (**3b**, **3c**) to give the product in a yield of 67−81% and 81−86% ee (entries 7−9, Table 2). The addition of phenylacetylene (**3a**) to

thiophenyl glyoxylate (**2b**) gave the product in 93% yield and 73% ee (entry 4, Table 2). When the reaction was performed with a primary alkyl-substituted glyoxylate, such as ethyl propionate (**2d**), a very low chemical yield was observed (entry 10, Table 2). This can be explained by the easy formation of the enolate of ketone with the base, which inhibited the addition reaction. When the substrate was switched to a tertiary alkyl group, excellent chemical and optical yields were observed (entries 11 and 12, Table 2). Similar results were obtained when (−)-*N*-methylephedrine **5** was examined as ligand in this reaction (entry 2, Table 2; the rotation data were in contrast to those with ligand (1*S*,2*S*)-**1**). $Zn(OSO_2CHF_2)_2$ gave the product in moderate ee (entry 3, Table 2).

Compound **4h** was hydrogenated with Pd−C under hydrogen at 4 atm to provide α-hydroxyl ester **6** (Scheme 2).[7] Comparing the optical rotation of the synthesized **6** (−26, *c* 0.26, $CHCl_3$) with that of ethyl (*S*)-2-hydroxy-2-methyl-4-phenyl-butyrate, which has been reported to be +29.6 (*c* 2.4, $CHCl_3$),[8] the absolute stereochemistry of the tertiary asymmetric alcohol carbon in **4h** was assigned to be *R*.

In summary, we have described a practical method for the synthesis of optically active tertiary α-hydroxyl *β*-ynyl ester based on the addition of terminal alkynes to α-keto esters in the presence of a catalytic amount of (1*S*,2*S*)-**1** as ligand and $Zn(OTf)_2$ as an additive. These highly functional α-hydroxyl *β*-ynyl esters are valuable chiral synthons for the further preparation of complex chiral compounds. The fact that a tertiary α-hydroxyl carbon center can be generated under mild conditions in the presence of inexpensive ligands may lead to new opportunities in pharmaceutical synthesis.

Scheme 2. Hydrogenation Reaction of Compound **4h**



4h **6**

Acknowledgment. This work was financially supported by the State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Supporting Information Available: General catalytic reaction conditions and the structural data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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