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Asymmetric alkynylation of aldehydes with propiolates without high reagent loading and any additives†

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The asymmetric alkynylation of aliphatic and aromatic aldehydes with propiolates was mediated by dialkylzinc and a novel prolinol catalyst without high reagent loading and any additives, such as Ti(O*i*-Pr)$_4$, to give the corresponding γ-hydroxy-α,β-acetylenic esters with high enantiomeric excess of up to 95%.

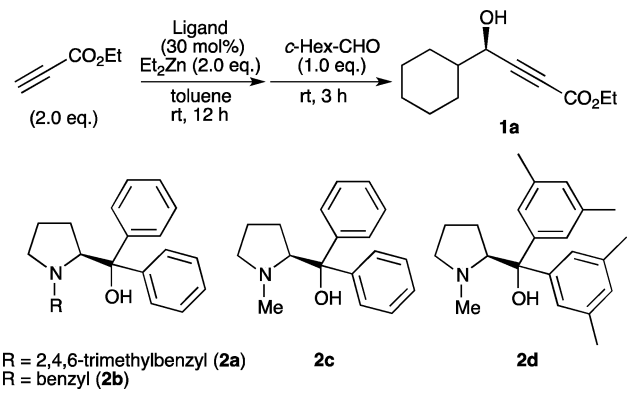
Chiral propargyl alcohols are versatile building blocks for fine chemicals, pharmaceuticals, and natural products.[1] A typical example is chiral γ-hydroxy-α,β-acetylenic esters, considered attractive molecules because they contain three functionalities: a hydroxyl group, an alkyne, and an ester, in a small structure. Many efficient syntheses that employed them as useful and versatile intermediates have been reported.[2,3] The two most common methods to prepare optically active γ-hydroxy-α,β-acetylenic esters are i) the asymmetric reduction of γ-oxo-α,β-acetylenic esters with a chiral reagent, and ii) the asymmetric alkynylation of aldehydes with propiolates. The latter has attracted widespread interest in recent years because it is able to achieve both new C–C bond formation and construction of a stereogenic centre. However, previous studies of the asymmetric alkynylation of aldehydes have concentrated on the addition of simple terminal alkynes, for example, phenylacetylene.[4] Difficulty arises in the asymmetric alkynylation using propiolate as the nucleophile because the reactivity of propiolate is greatly different from that of simple terminal alkynes.[5]

Recently, Pu and co-workers reported that BINOL and H$_8$-BINOL derivatives catalysed the Et$_2$Zn-mediated asymmetric alkynylation of aldehydes with methyl propiolate.[6] Wang's group developed the enantioselective addition of methyl propiolate to aromatic aldehydes with β-sulfonamide alcohol as the ligand.[7] Although previous studies, including those methods, gave products in good yields with high enantioselectivities, most of them required excess amounts of reagents and additives, such as Ti(O*i*-Pr)$_4$. Trost *et al.*[8] and Wang and co-workers[9] independently demonstrated the Me$_2$Zn-mediated enantioselective addition of methyl propiolate to aldehydes without any additives. However, their reactions still required excess amounts of Me$_2$Zn and propiolate. Herein, we disclose a dialkylzinc-mediated asymmetric alkynylation of aliphatic and aromatic aldehydes using propiolates, which is catalysed by a novel prolinol system and does not require any additives and high reagent loading.

We focused on a prolinol derivative for its potential use as a chiral ligand in the asymmetric alkynylation with propiolates, because there are many reports of the asymmetric alkylation and alkenylation of aldehydes with prolinol as the catalyst.[10] However, to our knowledge, there are few studies of the asymmetric alkynylation of aldehydes using prolinol as the catalyst.[8]

First, we attempted to perform the enantioselective addition of ethyl propiolate to cyclohexanecarbaldehyde using (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM, **2c**) as the ligand, and obtained chiral γ-hydroxy-α,β-acetylenic ester **1a** in good yield with moderate enantioselectivity (88%, 69% ee) (Table 1, Entry 3).[11] At the same time, Zhang and co-workers reported the enantioselective addition of alkynes to aldehydes using *N*-benzyl prolinol as the catalyst.[12] As the reaction using propiolates was not

Table 1 Ligand screening in the model reaction



Entry	Ligand	Yield (%)[a]
1	**2a**	75 (50% ee)
2	**2b**	80 (51% ee)
3	**2c**	88 (69% ee)
4	**2d**	87 (75% ee)

[a] Determined by ^{1}H NMR. Ee was determined by HPLC.

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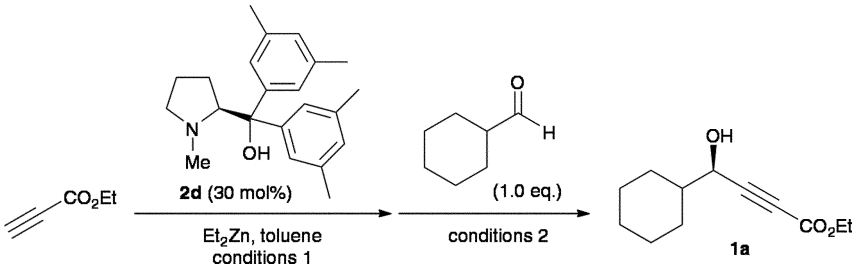
Table 2 Optimization of reaction conditions



					Conditions 1		Conditions 2		
Entry	Propiolate (eq.)	Et_2Zn (eq.)	Ligand (eq.)	Solvent	T/°C	Time (h)	T/°C	Time (h)	Yield (%)[a]
1	2.0	2.0	0.3	toluene	rt	12	rt	3	87 (75% ee)
2	2.0	2.0	0.3	toluene	rt	0	rt	3	89 (89% ee)
3	1.0	2.0	0.3	toluene	rt	0	rt	1.5	84 (91% ee)
4	1.0	1.2	0.3	toluene	rt	0	rt	3	84 (89% ee)
5	1.0	1.1	0.3	toluene	rt	0	rt	5	73 (89% ee)
6	1.0	1.2	0.3	toluene	0	0	0	5	<56 (91% ee)
7	1.0	1.2	0.3	toluene	40	0	40	3	83 (86% ee)
8	1.0	1.2	0.4	toluene	rt	0	rt	3	79 (89% ee)
9	1.0	1.2	0.1	toluene	rt	0	rt	3	72 (91% ee)
10	1.0	1.2	0.3	CH_2Cl_2	rt	0	rt	3	66 (81% ee)
11	1.0	1.2	0.3	*n*-hexane	rt	0	rt	3	70 (77% ee)
12	1.0	1.2	0.3	Et_2O	rt	0	rt	3	63 (81% ee)
13	1.0	1.2	0.3	THF	rt	0	rt	3	trace

[a] Determined by ^{1}H NMR. Ee was determined by HPLC.

reported in their letter, we examined the asymmetric alkynylation with their chiral ligands (**2a** and **b**).

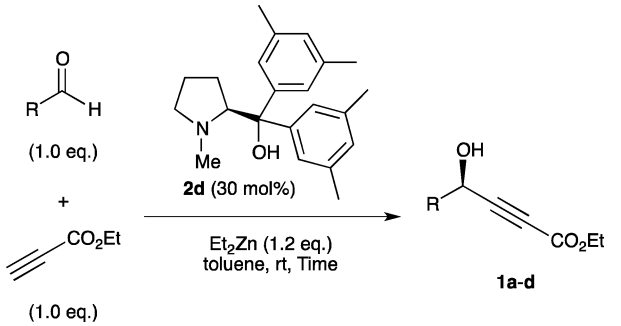
The reactions catalysed by their chiral ligands (**2a** and **b**) gave γ-hydroxy-α,β-acetylenic esters in good yields, but the enantioselectivities were low (~50% ee) (Entries 1 and 2). As a result of several investigations, we found that a novel *N*-methyl prolinol derivative with two 3,5-dimethylphenyl moieties (**2d**)[13] catalysed the asymmetric alkynylation in high yield with good enantioselectivity (Entry 4).

Table 2 shows the optimization of the reaction conditions. To a solution of 30 mol% of ligand **2d** in toluene, Et_2Zn (2.0 equiv.) and ethyl propiolate (2.0 equiv.) were added at room temperature. After 12 h, cyclohexanecarbaldehyde (1.0 equiv.) was added and the reaction mixture was stirred for 3 h, giving chiral propargyl alcohol **1a** in good yield with high enantioselectivity (Entry 1). The previously reported dialkylzinc-mediated alkynylation of aldehydes required a mixing step prior to the addition of aldehydes to prepare an alkynylzinc species. Without this step, the alkyl adduct was obtained as a by-product[14] because chiral ligands, such as BINOL[15] and β-sulfonamide alcohol,[16] would catalyse the addition of dialkylzinc to aldehydes. Surprisingly, the reaction that did not include a mixing step prior to the addition of aldehyde in the presence of **2d** gave propargyl alcohol **1a** in high yield, and no ethyl adduct was detected (Entry 2). Furthermore, this improvement not only simplified the reaction but also increased the enantioselectivity. We surmise that ligand **2d** can catalyse the formation of an alkynylzinc species more efficiently than previous ligands and therefore, the long mixing time afforded dialkynylzinc species, thereby decreasing the enantioselectivity.[14] Fortunately, the efficiency of our catalyst **2d** enabled the reduction of the amounts of Et_2Zn and propiolate (Entries 2–5). The reaction using 1.0 equiv. of propiolate and 1.2 equiv. of Et_2Zn gave almost the same result as that of Entry 2 (Entry 4). When the reaction temperature was lowered to 0 °C, the yield was decreased (Entry 6). On the other hand, there was no significant change in both yield and selectivity when the reaction was conducted at 40 °C compared with the case at room temperature (Entry 7). Increasing the amount of **2d** did not improve yield or selectivity (Entry 8), and the yield in the reaction using 0.1 equiv. of **2d** was reduced (Entry 9). The use of CH_2Cl_2, *n*-hexane, and Et_2O instead of toluene decreased both yield and enantioselectivity, whereas the reaction in THF hardly occurred (Entries 10–13).

Under the above optimal conditions (Table 2, Entry 4), we examined the alkynylation of aliphatic aldehydes with ethyl propiolate (Table 3). The reaction with propionaldehyde gave alcohol **1b** in moderate yield but with high enantioselectivity (Entry 1). Isobutylaldehyde gave the corresponding alcohol **1c** in good yield with high enantioselectivity (Entry 3). The use of a bulky aldehyde, pivalaldehyde, resulted in only a small decrease in enantioselectivity (Entry 4).

Next, we examined the alkynylation of aromatic aldehydes (Table 4). The asymmetric alkynylation of benzaldehyde with ethyl propiolate under the optimal conditions afforded the desired alkynylated compound **1e** with high enantioselectivity, but the yield was low (32%) because the conditions gave an ethylation product (44%) as the main product (Entry 1). The use of Me_2Zn in place of Et_2Zn dramatically decreased the alkyl adduct (3%) and increased the yield of **1e** to 52% (Entry 2).[17] By increasing the reagent loading (Me_2Zn and ethyl propiolate) to 2.0 equiv., the yield of **1e** was improved to 78% with high enantioselectivity (95% ee) (Entry 3). Having established the optimal reaction conditions for aromatic aldehydes, we investigated the alkynylation of various

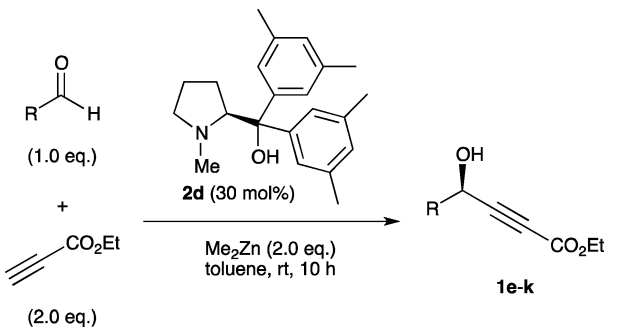
Table 3 Asymmetric alkynylation of aliphatic aldehydes[a]



Entry	Aldehyde	Time (h)	Yield (%)[b]	Selectivity[c]
1	Et	2	63 (**1b**)	89% ee (*R*)
2	*c*-Hex	3	84[d] (**1a**)	89% ee (*R*)
3[e]	*i*-Pr	4	76 (**1c**)	92% ee (*R*)
4	*t*-Bu	4	69 (**1d**)	83% ee (*R*)

[a] Aldehyde (1.0 mmol), ethyl propiolate (1.0 mmol), Et_2Zn (1 M solution in *n*-hexane, 1.2 mmol), and **2d** (0.3 mmol) in toluene (6 mL) were stirred at rt under Ar. [b] Isolated yield. [c] Ee was determined by HPLC. The stereochemistry of the products was confirmed by the modified Mosher method. [d] Determined by ^1H NMR. [e] The reaction was carried out with 3.0 mmol of aldehyde.

Table 4 Asymmetric alkynylation of aromatic aldehydes[a]



Entry	Aldehyde	Yield (%)[b]	Selectivity[c]
1[d]	C_6H_5	32 (**1e**)	>99% ee
2[e]		52 (**1e**)	95% ee
3		78 (**1e**)	95% ee (*R*)[f]
4	*o*-Br-C_6H_4	76 (**1f**)	93% ee (*S*)
5	*m*-Br-C_6H_4	71 (**1g**)	95% ee
6	*p*-Br-C_6H_4	75 (**1h**)	92% ee
7	*p*-MeO-C_6H_4	54 (**1i**)	90% ee (*R*)
8	*p*-CO_2Me-C_6H_4	71 (**1j**)	91% ee (*R*)
9	2-Furyl	66 (**1k**)	76% ee

[a] Aldehyde (1.0 mmol), ethyl propiolate (2.0 mmol), Me_2Zn (1 M solution in *n*-hexane, 2.0 mmol), and **2d** (0.3 mmol) in toluene (6 mL) were stirred at rt under Ar. [b] Isolated yield. [c] Ee was determined by HPLC. The stereochemistry of the products was confirmed by the modified Mosher method after transformation to the corresponding allyl alcohols. For details, see Electronic Supplementary Information. [d] Ethyl propiolate (1.0 eq.) and Et_2Zn (1.2 eq.) were used. [e] Ethyl propiolate (1.0 eq.) and Me_2Zn (1.2 eq.) were used. [f] Absolute configuration was determined by comparing the optical rotation with the literature value after conversion into the known methyl ester. For details, see Electronic Supplementary Information.

aromatic aldehydes. The reactions of benzaldehydes containing a bromine atom at the *ortho*-, *meta*-, and *para*-positions gave good yields and high enantioselectivities, respectively (Entries 4–6). Both *p*-anisaldehyde and *p*-formylphenyl acetate, respectively, were converted into the corresponding alcohols **1i** and **1j** with high enantioselectivities, but the yield of the former was moderate (54%) because of less reactivity due to the electron-donating substituent (Entries 7 and 8). The desired product was also obtained when heterocyclic aldehyde was employed as the substrate, although the yield and the selectivity were decreased (Entry 9). The results showed that this catalytic system has a broad generality for aliphatic and aromatic aldehydes.

Asymmetric alkynylation in the presence of chiral prolinol **2d** afforded (*R*)-propargyl alcohol. The absolute configuration of the newly created chiral centre is predictable based on the model (Fig. 1). The model is analogous to that proposed by Noyori and co-workers for the Me_2Zn addition to aldehydes.[18] The carbonyl oxygen atom of the aldehyde coordinates to the zinc of the bimetallic complex generated from the chiral ligand, zinc acetylide, and Et_2Zn, and then an alkynyl group attacks the carbonyl carbon of the aldehyde as shown, giving an (*R*)-isomer.

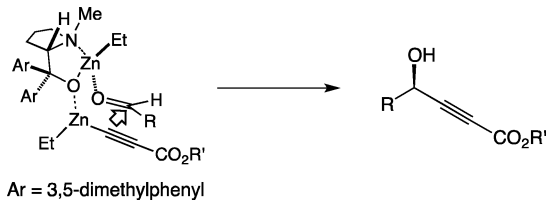


Fig. 1 Model predicting the stereochemistry.

In conclusion, we have demonstrated the enantioselective addition of propiolates to aliphatic and aromatic aldehydes in the presence of a novel prolinol catalyst without high reagent loading and any additives. Our chiral ligand systems make it possible to prepare easily chiral γ-hydroxy-α,β-acetylenic esters. It is interesting to catalyse the asymmetric addition of propiolates to aldehydes by structurally simple ligand **2d** with good enantioselectivity. The scope, mechanism, and synthetic application are under investigation.

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