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Enantioselective synthesis of α-aminopropargylphosphonates

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Abstract—α-Aminopropargylphosphonates have been synthesized for the first time in good yields and enantiomeric excesses (up to 81% ee) by using a copper(I)–pybox complex as the catalyst.

α-Aminophosphonic acids, as structural mimics of α-amino acids, exhibit a broad spectrum of biological activities.[1–3] These compounds have already been found to act as antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already commercialized.[1–3] As is the case of α-amino acids, the absolute configuration of the amino-substituted α-carbon of α-aminophosphonic acids have significant influence on the observed biological activities.[2] Consequently, the asymmetric synthesis of α-aminophosphonates has been the focus of recent research.[4] Besides the enzymatic resolution of racemic α-aminophosphonates,[3] several chemical methods[1,4] have been reported for the synthesis of enantioenriched α-aminophosphonates, either diastereoselectively or enantioselectively. Among the reported chemical methods, Mannich-type addition of phosphorus nuleophiles to imines (i.e., C–P bond formation) represents one of the most useful methods for obtaining enantioenriched α-aminophosphonates.[5] Alternatively, optically active α-aminophosphonates may be obtained through the addition of carbon nucleophiles to iminophosphonates (i.e., C–C bond formation),[6,7] as exemplified by the recent elegant work from the Kobayashi group.[7] Nonetheless, this synthetic pathway has not been fully explored.

Synthesis of propargylamines from imines through the direct addition of terminal alkynes by using metal complexes is well known in the literature.[8] Because of our continued interests in the synthesis of enantioenriched α-substituted phosphonate derivatives,[9] recently we extended this reaction to α-iminophosphonates and developed the first general synthesis of α-aminopropargylphosphonates by using silver(I) or copper(I) salts as the catalysts.[10] These results represent another example of carbon–carbon bond formation for the synthesis of α-aminophosphonates. Because the alkynyl triple bond may be readily elaborated to induce other functional groups, the products of this novel reaction, α-aminopropargylphosphonates, should be versatile substrates for the synthesis of other α-aminophosphonate derivatives. Additionally, these compounds may possess interesting biological activities by themselves, although they have not been evaluated for this purpose in the past.

Since silver(I) or copper(I) salts are good catalysts for the addition of terminal alkynes to α-iminophosphonates,[10] it is quite reasonable to assume that an enantioselective version of this reaction may be achieved by adding a proper chiral ligand. In the current Letter, we wish to report our preliminary results on the first enantioselective synthesis of α-aminopropargylphosphonates through the direct addition of terminal alkynes to an α-iminophosphonate by using a copper(I)–pybox complex as the catalyst. This is the first example where α-iminophosphonate is used as a substrate in the direct enantioselective alkynylation.[8]

By using phenylacetylene (**11a**) and diethyl [(4-methoxyphenyl)imino]methylphosphonate (**12**)[10] as the substrates and Cu(I) triflate toluene complex,[11] we first screened several bisoxazoline ligands (Fig. 1) for their ability of asymmetric induction. The results are summarized in Table 1.

Keywords: Aminopropargylphosphonate; Alkyne; Iminophosphonate; Copper(I) triflate; Pybox; Enantioselective; Phosphonate.
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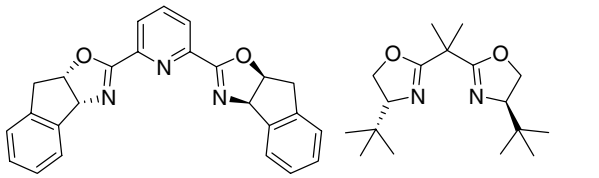
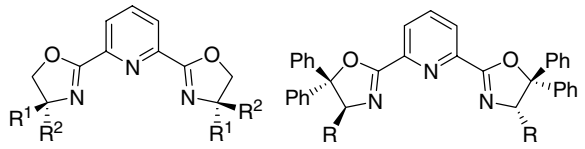


1 **2**



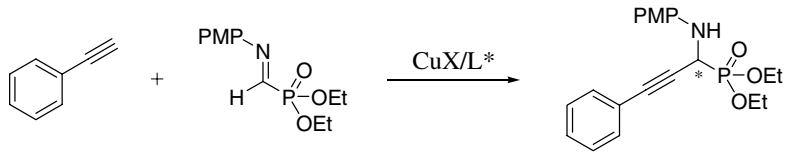
3. R^1 = H, R^2 = Me
4. R^1 = H, R^2 = Et
5. R^1 = H, R^2 = *i*-Pr
6. R^1 = *t*-Bu, R^2 = H
7. R^1 = H, R^2 = Ph

8. R = Me
9. R = *i*-Pr
10. R = *t*-Bu

Figure 1. Chiral bisoxazolidine ligands screened for the alkynylation of α-iminophosphonate.

Although the pybox ligand **1**[12] was reported to be the best one for a similar reaction using α-iminocarboxylate as the substrates,[8q] it led to a poor enantioselectivity of only 27% of the desired α-aminopropargylphosphonate product (**13a**) in our hand. Nonetheless, the product was obtained in a good yield of 72% (entry 1). Bidentate bisoxazoline ligand **2**[13] gave even worse enantioselectivities (20% ee, entry 2). Further screening of some C_2-symmetric 4,4′-disubstitued pybox ligands (**3**–**7**)[13,14] revealed that both the sense and the extent of the enantioselectivity of this reaction are dependent on the size of the substituents at the 4 and 4′ positions of the oxazoline ring (entries 3–7). With the size of the substituents increases from Me (**3**), to Et (**4**), and then to *i*-Pr (**5**), the enantioselectivity gradually increases from 40% to 53% (entries 3–5). However, further increasing the size to *t*-Bu group (**6**) leads to poorer enantioselectivity (40% ee, entry 6). The opposite enantiomer was obtained as the major product in this case. However, it should be pointed out that ligand **6** has an opposite stereochemistry [(*S*,*S*)] as compared to ligands **3**–**5** [(*R*,*R*)] and, therefore, the sense of stereoselectivity actually remains the same as ligands **3**–**5**. In contrast, the phenyl-substituted ligand (*R*,*R*)-**7** leads to *an opposite sense* of stereoselectivity and a poor ee value of the product (22%, entry 7). These results indicate that there are probably two competing orientations of substrate **12** when it approaches the metal–ligand complex. Which one of them dominates is dependent on the substituents on the oxazoline rings. Such a phenomenon has been observed previously by Singh and co-workers in the

Table 1. Ligand screening and reaction condition optimizations[a]



11a **12** **13a**

Entry	Ligand	CuX	Solvent	Reaction time (h)	Yield[b] (%)	ee[c] (%)
1	**1**	$(CuOTf)_2$·toluene	$CHCl_3$	10	72	27
2	**2**	$(CuOTf)_2$·toluene	$CHCl_3$	10	55	20
3	**3**	$(CuOTf)_2$·toluene	$CHCl_3$	10	81	40
4	**4**	$(CuOTf)_2$·toluene	$CHCl_3$	10	80	47
5	**5**	$(CuOTf)_2$·toluene	$CHCl_3$	10	78	53
6	**6**	$(CuOTf)_2$·toluene	$CHCl_3$	10	73	40[e]
7	**7**	$(CuOTf)_2$·toluene	$CHCl_3$	10	88	22[e]
8	**8**	$(CuOTf)_2$·toluene	$CHCl_3$	2	93	21[e]
9	**9**	$(CuOTf)_2$·toluene	$CHCl_3$	2	90	68[e]
10	**10**	$(CuOTf)_2$·toluene	$CHCl_3$	2	91	74[e]
11	**10**	$(CuOTf)_2$·benzene	$CHCl_3$	2	80	74[e]
12	**10**	$Cu(OTf)_2$	$CHCl_3$	10	72	74[e]
13	**10**	$Cu(MeCN)_4PF_6$	$CHCl_3$	10	—	—
14	**10**	$(CuOTf)_2$·toluene	CH_2Cl_2	2	81	74[e]
15	**10**	$(CuOTf)_2$·toluene	Toluene	2	45	73[e]
16	**10**	$(CuOTf)_2$·toluene	THF	2	78	65[e]
17[d]	**10**	$(CuOTf)_2$·toluene	$CHCl_3$	10	88	73[e]
18[f]	**10**	$(CuOTf)_2$·toluene	$CHCl_3$	10	92	74[e]

[a] Experimental conditions: Unless otherwise specified, all reactions were conducted with imine **12** (136.0 mg, 0.5 mmol), phenyl acetylene (153 mg, 1.5 mmol), CuX (0.05 mmol, 10 mol %), and the ligand (0.055 mmol, 11 mol %) in anhydrous $CHCl_3$ (3.0 mL) at room temperature for the specified reaction time.

[b] Isolated yields after column chromatography.

[c] Enantiomeric excess was determined by chiral HPLC analysis on a Chiralcel OJ-H column; the absolute configuration of the product was not determined.

[d] The reaction was carried out at 0 °C.

[e] The opposite enantiomer was obtained as the major product.

[f] With 2 mol % of $(CuOTf)_2$·toluene complex and 2.1 mol % of **10**.

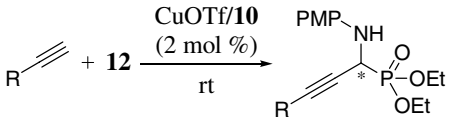
alkynylation of imines with these ligands.[8n] In order to achieve good enantioselectivity in the reaction, one of these orientations should be avoided, possibly through finely tuning the steric environment of the chiral ligand.[8n] On the basis of this assumption, (*S*,*S*) ligands **8**–**10**[15,16] were synthesized, with four phenyl groups at the 5 and 5′ positions of the oxazoline ring to bias the substrate orientations. Except for ligand **8** (entry 8), which has smaller methyl groups at the 4 and 4′ positions, these ligands indeed provide better ee values of the product. For example, ee values of 68% and 74% were obtained for ligand **9** (entry 9) and ligand **10** (entry 10), respectively. Again, the sense of stereoselectivity of these ligands is the same as that of ligands **3**–**6**.

The effect of copper salts on this reaction was then examined by using the best pybox ligand **10**. The results showed that both Cu(I) triflate benzene complex (entry 11) and Cu(II) triflate (entry 12) produce the same level of enantioselectivity of the product as Cu(I) triflate toluene complex does (entry 10), except that Cu(II) triflate is less reactive: lower yield was obtained at longer reaction time (entry 12). In contrast, Cu(I) hexafluorophosphate acetonitrile complex failed to catalyze the reaction completely (entry 13). Thus, the combination of Cu(I) triflate toluene complex and ligand **10** was identified as the best catalyst in terms of both reactivity and enantioselectivity. The solvent effects on this reaction were also studied. Among the common organic solvents, $CHCl_3$ proved to be the best one for this reaction (entry 10), whereas CH_2Cl_2 (entry 14), toluene (entry 15), and THF (entry 16) all gave either lower yields and/or poorer enantioselectivities. Interestingly, lowering the reaction temperature to 0 °C showed no improvement in the enantioselectivity of this reaction (entry 17). Gratifyingly, it was found that 10 mol % loading the catalyst is unnecessary, since the reaction with only 2 mol % catalysts gave similar results as those with 10 mol % (entry 18).

Under the optimized reaction conditions (2 mol % of catalyst loading, $CHCl_3$ as solvent at room temperature) the scope of the reaction was examined with various terminal alkynes.[17] The results are collected in Table 2. Besides phenyl acetylene (entry 1), other aryl-substituted terminal alkynes also participate in this reaction. In the case of mono-substituted phenylacetylenes, the presence of either an electron-donating or withdrawing substituent in the *ortho*, *meta* or *para* positions has almost no influence on the reactivities or the enantioselectivities of the reaction (entries 2–9). The highest enantioselectivity (81% ee) was obtained with the difluorinated phenylacetylene **11j** (entry 10). 1-Ethylenenaphthalene also participates in this reaction, and the desired product (**13k**) was obtained in 72% yield and 60% ee (entry 11). Aliphatic terminal alkynes, such as 1-heptyne and 4-phenyl-1-butyne also afford the expected α-aminopropargylphosphonates in good yields with similar enantioselectivities (64% and 67% ee, respectively; entries 12 and 13).

In summary, we have developed the first enantioselective method for the synthesis of enantioenriched α-aminopropargylphosphonates. In general, high yields and good levels of asymmetric induction (60–81% ee) may be achieved by using Cu(I) triflate and pybox ligand **10**. A low catalyst loading of only 2 mol % is necessary to achieve the desired transformations. The products

Table 2. Enantioselective synthesis of α-aminopropargylphosphonates (**13a**–**m**) from terminal alkynes (**11a**–**m**) and imine **12**[a]



11 **13a**

Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	Ph	**13a**	92	74
2	4-BrC_6H_4	**13b**	88	74
3	2-BrC_6H_4	**13c**	85	68
4	4-ClC_6H_4	**13d**	90	74
5	4-FC_6H_4	**13e**	91	68
6	4-$CF_3C_6H_4$	**13f**	81	75
7	4-$CH_3C_6H_4$	**13g**	86	75
8	3-$CH_3C_6H_4$	**13h**	80	74
9	4-$CH_3OC_6H_4$	**13i**	88	70
10	3,5-$F_2C_6H_3$	**13j**	82	81
11	Naphth-1-yl	**13k**	72	60
12[d]	$CH_3(CH_2)_4$	**13l**	69	64
13[d]	$PhCH_2CH_2$	**13m**	56	67

[a] Experimental conditions: unless otherwise indicated, all reactions were conducted with imine **12** (136.0 mg, 0.50 mmol), acetylene (1.5 mmol), $(CuOTf)_2$·toluene (5.2 mg, 0.010 mmol, 2.0 mol %), and **10** (7.0 mg, 0.011 mmol, 2.1 mol %) in anhydrous $CHCl_3$ (3.5 mL) at room temperature for 10 h.

[b] Yields of isolated products after column chromatography.

[c] Enantiomeric excess was determined by chiral HPLC analysis on either a Chiralpak AD-H, or a Chiralcel OJ-H, or a Chiralcel OD-H column; the absolute configurations of the products were not determined.

[d] The reaction time was 24 h.

should be useful for the synthesis of other enantio-enriched α-aminophosphonic acid derivatives. The mechanism of this reaction is currently under study and will be disclosed in due time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.124.

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17. *General procedure for the synthesis of α-amino-propargylphosphonates*: To an oven-dried 10-mL round-bottomed flask was added $(CuOTf)_2$·toluene complex (0.01 mmol, 2.0 mol %), compound **10** (7.0 mg, 0.011 mmol, 2.1 mol %) and $CHCl_3$ (3.0 mL). After the mixture was stirred at room temperature for 2 h, a solution of imine **12** (136.0 mg, 0.50 mmol) in $CHCl_3$ (0.5 mL) was added while vigorous stirring, followed immediately by the terminal alkyne (1.5 mmol). The mixture was further stirred for 10 h at room temperature. After removing the solvent, the crude product was subjected to flash column chromatography (silica gel, 6:4 hexane/EtOAc) for purification, which gives the desired products as pure compounds (for NMR spectroscopic data of the products, see Ref. 10).