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Copper(I)-Catalyzed Asymmetric Addition of Terminal Alkynes to β-Imino Esters: An Efficient and Direct Method in the Synthesis of Chiral β^3-Alkynyl β^{2,2}-Dimethyl Amino Acid Derivatives

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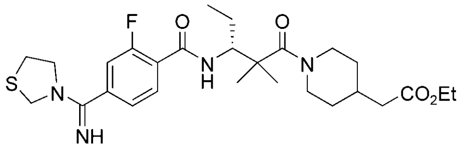
Abstract: The first catalytic asymmetric addition of terminal alkynes to β-imino esters was carried out using chiral copper(I) complexes as catalysts under mild reaction conditions, providing an efficient and direct synthetic approach to β^3-alkynyl β^{2,2}-dimethyl amino esters with yields of 73–97% and 48–90% *ee*. The rich chemistry of the alkynyl functionality makes the present method a powerful and versatile approach to a wide range of optically active β^{2,2}-dimethyl amino acid derivatives.

Keywords: asymmetric alkynylation; asymmetric catalysis; copper; enantioselectivity; β-imino esters

β-Amino esters are useful building blocks for the synthesis of many nitrogen-containing biologically important compounds such as β-lactams; the development of effective catalytic methods for the enantioselective synthesis of β-amino esters is a subject of active research.[1] The asymmetric Mannich reaction constitutes one of the most powerful tools for the synthesis of chiral β-amino acids.[2] Some typical "Mannich donors" include silicon enolates, metal enolates, ketones and aldehydes. Asymmetric Mannich-type reactions involving addition of silyl enolates to aromatic aldimines catalyzed by chiral Lewis acid catalysts have been extensively investigated, and β^{2,2,3}-trisubstituted β-amino esters can be obtained in good yields with moderate to high enantiomeric excesses.[3] Recently, proline and derivatives have emerged as effective organocatalysts for asymmetric Mannich reactions of ketones or equivalents thereof and imines.[4] Alternatively, imino-Reformatsky reactions[5] have recently been exploited for enantioselective β-amino ester synthesis. Some notable achievements have been made by Cozzi and co-workers in developing a one-pot, three-component coupling protocol for enantioselective imino-Reformatsky reactions.[6]

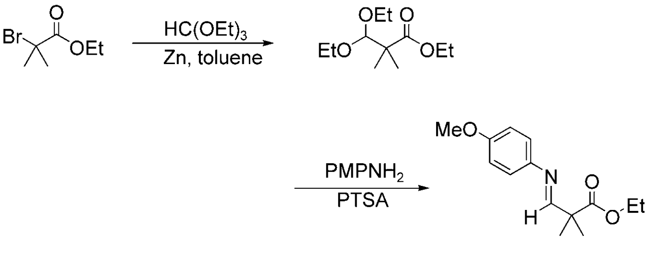
Metal-catalyzed alkynylation of imines is a direct and convenient strategy for the synthesis of propargylamines.[7] Recently, we reported the catalytic asymmetric alkynylation of α-imino esters for the preparation of optically active propargylic α-amino acids. Using Cu(I) as catalyst and chiral bis(oxazolinyl)pyridine (Pybox) as ligand, the addition of 1-octyne to α-imino esters was achieved in up to 91% *ee*.[8] Based on this finding, we anticipated that the analogous alkynylation of β-imino esters would afford enantioenriched propargylic β-amino acids. In this work, we present our investigation on the Cu-catalyzed enantioselective addition of terminal alkynes to 3-(4-methoxyphenylimino)-2,2-dimethylpropionate, and β^3-alkyne β^{2,2}-dimethyl amino esters were formed in up to 90% *ee*. According to the literature, 3-substituted-2,2-dimethyl-β-amino acid residues are useful linear templates for conformationally restricted peptidomimetics, and they possess interesting pharmacological activities.[9] For example, ethyl *N*-(3-{2-fluoro-4-[thiazolidin-3-yl(imino)methyl]benzoyl}amino-2,2-dimethylpentanoyl)piperidine-4-acetate (NSL-96184) was reported to be a highly potent and orally active fibrinogen receptor antagonist (Figure 1).[10]

By means of a modified Reformatsky reaction (Scheme 1),[11] treatment of ethyl bromoisobutyrate with zinc and triethyl orthoformate afforded 3,3-diethoxy-2,2-dimethylpropionic acid ethyl ester in 78% yield. Condensation of 3,3-diethoxy-2,2-dimethylpro-



NSL-96184

Figure 1. The structure of NSL-96184.



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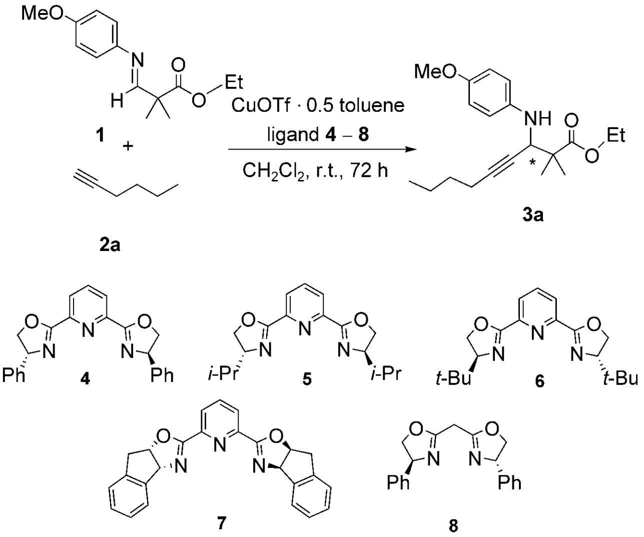
Scheme 1. Synthesis of 3-(4-methoxyphenylimino)-2,2-dimethylpropionic acid ethyl ester **1**.

pionic acid ethyl ester with *p*-anisidine in the presence of *p*-toluenesulfonic acid monohydrate (PTSA) gave 3-(4-methoxyphenylimino)-2,2-dimethylpropionic acid ethyl ester **1** in 91% yield.

When β-imino ester **1** (0.25 mmol) was treated with 1-hexyne **2a** (0.5 mmol), CuOTf0.5toluene (0.025 mmol) and pybox ligand **4** (0.025 mmol) in CH_2Cl_2 (1 mL) at room temperature for 72 h, **3a** was produced in 87% yield and 69% *ee* (Table 1, entry 1). The activity of other pybox derivatives for the alkynylation reaction has also been examined. As shown in Table 1, the best results (89% yield, 87% *ee*) were obtained when pybox ligand **6** containing *t*-Bu substituents was used (entry 3). Other pybox derivatives bearing *i*-Pr (ligand **5**) or indanyl (ligand **7**) groups produced **3a** in lower enantioselectivity (*ca.* 68%, entries 2 and 4), while the bidentate bis(oxazoline) ligand **8** gave 73% yield but a racemic product (<1% *ee*). Analogous to our previous work,[8] other ligands such as Binap, Quinap and MonoPhos phosphoramidites failed to give comparable results.

Table 1. Cu-catalyzed enantioselective addition of 1-hexyne to β-imino ester **1**.[a]



Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**4**	87	69
2	**5**	68	67
3	**6**	89	87
4	**7**	87	69
5	**8**	73	1

[a] All the reactions were carried out in a 0.25 mmol scale of **1** using 2 equiv. of alkyne **2a** in 1.0 mL CH_2Cl_2 with 10 mol% Pybox and 10 mol% CuOTf·0.5toluene at room temperature.

[b] Isolated yield.

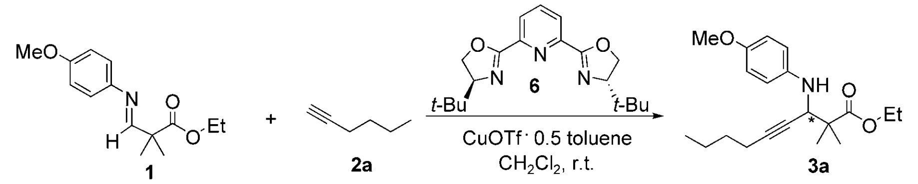
[c] Determined by chiral HPLC using a Chiralpak AD-H column.

Reiser reported the Michael addition of indole to benzylidene malonate catalyzed by a copper catalyst containing bis(oxazoline) ligands in which the excess of ligand with respect to the metal was detrimental to enantioselectivity.[12] According to our earlier reports on the alkynylation of α-imino esters, the ligand-to-metal ratio was found to have a profound influence on the enantioselctivity.[8c] In this work, the effect of the ligand-to-metal ratio on the alkynylation of β-imino ester **1** has been investigated. As shown in Table 2, a ligand-to-metal ratio > 1:1 resulted in sluggish reactions. For instance, with a ligand-to-metal ratio = 1.5:1, the product **3a** was obtained in 53% yield after seven days of reaction (entry 1). Interestingly, when a ligand-to-metal ratio of 0.75:1 was employed, **3a** was obtained in 88% yield on day 1 and 97% yield on day 2. An optimum ligand-to-metal ratio was found to be 0.5:1 and **3a** was produced quantitatively after two days of reaction (entry 5). Notably, ligand-to-metal ratios <0.5:1 also led to sluggish reactions (entries 6 and 7). However, the enantioselectivity of the alkynylation reaction was rather insensitive to the ligand-to-metal ratio.

Table 3 depicts the effect of solvent on the Cu-catalyzed enantioselective addition of 1-hexyne to β-imino ester **1.** When toluene and EtOAc were employed, **3a** was obtained in *ca.* 65% yield. Other solvents such as THF, hexane, DCE and CH_2Cl_2 afforded better yields (>80%) of **3a**. Considering both the yield and enantioselectivity, we chose CH_2Cl_2 as the solvent for further studies.

With the optimized conditions in hand, the scope of alkynes in the reaction system was examined, and the results are summarized in Table 4. Both aliphatic alkynes and aromatic alkynes reacted smoothly with

Table 2. Effects of different ligand-to-Cu(I) ratio on reactivity and enatioselectivity.[a]



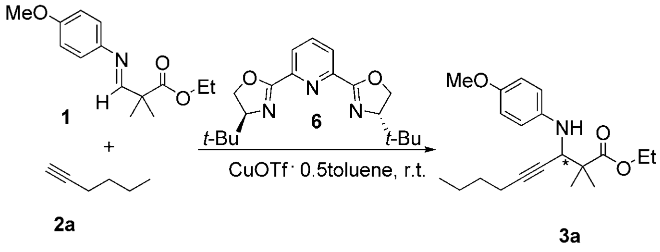
Entry	Ratio of **6** to Cu	Yield[b] [%]				*ee* [%][c]
		1 Day	2 Days	3 Days	7 Days	
1	1.5:1	14	29	36	53	88
2	1.25:1	26	48	60	90	88
3	1:1	60	88	95	/	87
4	0.75:1	88	97	/	/	87
5	0.5:1	94	100	/	/	87
6	0.25:1	66	90	95	/	85
7	0.125:1	43	72	83	84	83

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equiv. of alkyne **2a** in 1.0 mL CH_2Cl_2 with 10 mol% CuOTf·0.5 toluene at room temperature.

[b] Determined by GC with tetradecane as internal standard.

[c] Determined by chiral HPLC using a Chiralpak AD-H column.

Table 3. Effects of the choice of solvent on the reactivity and enantioselectivity.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	THF	80	90
2	Toluene	68	86
3	Hexane	82	54
4	EtOAc	60	90
5	DCE	87	87
6	CH_2Cl_2	97	87

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equiv. of alkyne **2a** in 1.0 mL solvent with 10 mol% CuOTf·0.5 toluene at room temperature.

[b] Determined by GC with tetradecane as internal standard.

[c] Determined by chiral HPLC using a Chiralpak AD-H column.

β-imino ester, providing the corresponding alkynylation products with excellent yields and good *ee*. Methyl propiolate **2g** is very active and the reaction was complete within several hours. However, the *ee* is only 48% (entry 8), and a lower reaction temperature did not improve the enantioselectivity, but just dropped the yield. The wide scope of the alkynes, especially alkynes with some functional groups, makes this reaction attractive.

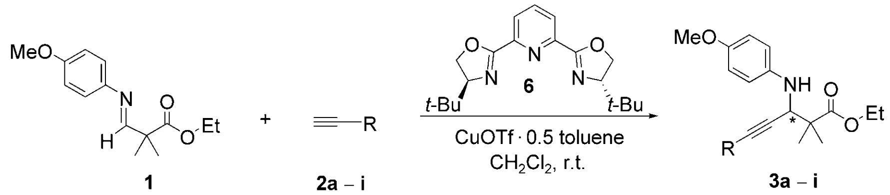
In conclusion, we have investigated the addition of terminal alkynes to β-imino esters, and developed the first catalytic enantioselective addition of terminal alkynes to β-imino esters. This reaction provides an efficient and direct synthetic approach to β^3-alkynyl $\beta^{2,2}$-dimethyl amino esters with 73–97% yields and 48–90% *ee*. The rich chemistry of alkynyl functionality makes the present method a powerful and versatile approach to a wide range of optically active $\beta^{2,2}$-dimethyl amino acid derivatives. The mechanism and synthetic applications of this efficient addition reaction are currently under investigation in our laboratory.

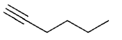
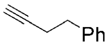
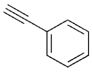
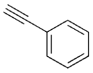
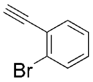
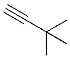
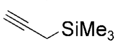
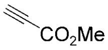
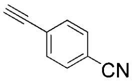
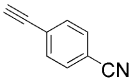
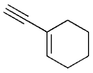
Experimental Section

Typical Procedure for Catalytic Asymmetric Alkynylation of β-Imino Esters

Pybox **6** (4.1 mg, 0.0125 mmol) and CuOTf·0.5 toluene (6.5 mg, 0.025 mmol) were added to a dried 5-mL reaction flask containing a magnetic stirring bar. CH_2Cl_2 (1.0 mL) was added, and the mixture was stirred at room temperature for 1 h. Then β-imino ester **1** (62 mg, 0.25 mmol) and alkyne (0.5 mmol) were sequentially added under vigorous stirring. The resulting solution was stirred at room temperature until the completion of the reaction, as monitored by TLC. The mixture was then passed through a short plug of silica gel which was subsequently washed with ether. The combined solutions were concentrated under vacuum. The purification of the residue by flash silica gel column chromatography

Table 4. Cu-catalyzed addition of alkynes to β-imino ester.[a]



Entry		Alkyne	Product	Yield [%][b]	*ee* [%][c]
1	**2a**		**3a**	97	87
2	**2b**		**3b**	93	75
3	**2c**		**3c**	96	83
4	**2c**		**3c**	84[d]	84
5	**2d**		**3d**	92	70
6	**2e**		**3e**	82	77
7	**2f**		**3f**	73	77
8	**2g**		**3g**	86	48
9	**2h**		**3h**	90	88
10	**2h**		**3h**	32[e]	85
11	**2i**		**3i**	81	77

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equiv. of alkyne **2a–i** in 1.0 mL CH_2Cl_2 with 5 mol% Pybox **6** and 10 mol% CuOTf·0.5toluene at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC using a Chiralpak AD-H or OD-H column.

[d] Reaction was performed in THF instead of CH_2Cl_2.

[e] Reaction was performed in THF and 60% **1** recovered.

yielded the corresponding alkynylation product (see Supporting Information for details).

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