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Diastereo- and Enantioselective Synthesis of Quaternary α-Amino Acid Precursors by Copper-Catalyzed Propargylation

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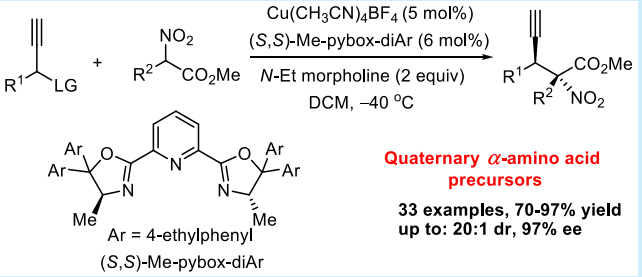
Supporting Information

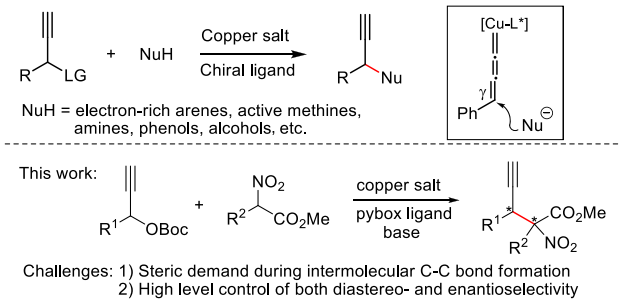
ABSTRACT: A diastereo- and enantioselective propargylic substitution reaction between propargylic carbonates and α-substituted nitroacetates catalyzed by a Cu–pybox complex is described. This method allows the preparation of a series of non-proteinogenic quaternary α-amino acid precursors featuring two contiguous stereogenic centers and a terminal alkyne moiety in high yields with good to excellent diastereo- and enantioselectivities in most cases. The propargylated adducts were elaborated into a diverse set of quaternary α-amino acid derivatives.



Because of the broad reactivity of alkynes, particularly in the celebrated click reaction, copper-catalyzed azide alkyne cycloaddition,[1] terminal-alkyne-functionalized α-amino acids have come to play an increasingly important role in medicinal chemistry and peptide chemistry.[2] However, the asymmetric catalytic synthesis of quaternary α-amino acids featuring a terminal alkyne moiety has been quite challenging and remains chemistry that is largely underdeveloped.[3] The design of new asymmetric catalytic reactions between nucleophilic α-amino acid precursors and electrophiles containing a terminal alkyne functionality leading to quaternary α-amino acids could serve to address this current limitation.[4]

Over the past few years, copper–allenylidene complexes generated from terminal alkyne propargylic alcohol derivatives and Cu-based chiral catalysts have emerged as versatile reactive species for the design of asymmetric propargylic substitution (APS) reactions with various nucleophiles, including C-based nucleophiles and heteroatom-based nucleophiles (Scheme 1).[5,6] Despite these achievements, the application of nucleophilic amino acid precursors to APS reactions remains an unmet synthetic challenge; indeed, to our knowledge this chemistry has yet to be reported. The most closely related examples were very recently reported by Niu and co-workers, wherein APS reactions of α-thio/α-oxacarboxylic acid precursors were realized through Cu/Zn or Cu/Ti catalysis.[6p] Such types of reactions, if successful, would install a terminal alkyne function on non-proteinogenic α-amino acids stereoselectively. Herein we report a highly efficient Cu-catalyzed APS of α-substituted nitroacetates[7] with *tert*-butyl propargylic carbonates, leading to structurally diverse quaternary α-amino acid precursors bearing a terminal alkyne moiety. Key to this development is the finding that pybox ligands bearing aryl groups at the 5-positions of the oxazoline rings allow for robust catalytic performance.[8]

Scheme 1. Copper-Catalyzed APS Reaction and Our Design for the Preparation of Quaternary α-Amino Acids



Initially, we examined the reaction between *tert*-butyl propargyl carbonate **1a** and methyl 2-nitro-2-phenylacetate (**2a**) promoted by a copper complex generated in situ from $Cu(CH_3CN)_4BF_4$ (10 mol %) and (*S*)-*sec*-butyl-pybox (**L1**) (12 mol %) at −10 °C with dichloromethane as the solvent and DIPEA as the base (Table 1, entry 1). To our delight, the reaction proceeded smoothly to afford the desired propargylation product **3aa** in high yield (83%), albeit with modest selectivities. Encouraged by this promising result, a set of other tridentate pybox ligands derived from commercially available

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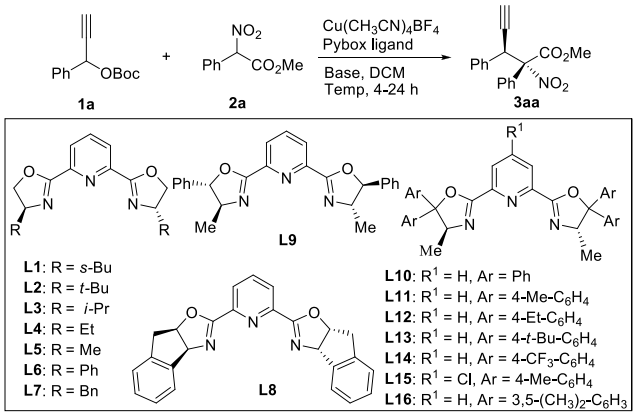
Table 1. Optimization of the Reaction Conditions[a]



entry	L	temp (°C)	base	yield (%)[b]	dr[c]	ee (%)[d]
1	**L1**	−10	DIPEA	83	2.3:1	59
2	**L2**	−10	DIPEA	78	3.3:1	15
3	**L3**	−10	DIPEA	82	1.4:1	65
4	**L4**	−10	DIPEA	77	1.1:1	78
5	**L5**	−10	DIPEA	78	1.4:1	83
6	**L6**	−10	DIPEA	80	3.8:1	40
7	**L7**	−10	DIPEA	81	1.5:1	27
8	**L8**	−10	DIPEA	trace	–	–
9	**L9**	−10	DIPEA	90	1.8:1	85
10	**L10**	−10	DIPEA	92	1.7:1	92
11	**L11**	−10	DIPEA	93	2.3:1	94
12	**L12**	−10	DIPEA	95	2.4:1	95
13	**L13**	−10	DIPEA	92	1.7:1	89
14	**L14**	−10	DIPEA	82	1.8:1	82
15	**L15**	−10	DIPEA	81	2.1:1	90
16	**L16**	−10	DIPEA	92	1.9:1	88
17	**L12**	−10	NEM[e]	95	3.2:1	95
18	**L12**	−40	NEM	94	7.6:1	97
19	**L12**	−50	NEM	70	7.6:1	97
20[f]	**L12**	−40	NEM	93	7.6:1	97

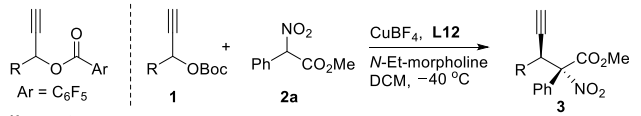
[a]General conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Cu-$(CH_3CN)_4BF_4$ (10 mol %), ligand (12 mol %), and DIPEA (2 equiv) in DCM (1 mL) at 10 °C for 4−24 h. [b]Yields of isolated pure **3aa**. [c]The dr of **3aa** was determined by ^{1}H NMR spectroscopy. [d]The ee of **3aa** was determined by chiral HPLC analysis. [e]NEM = *N*-ethylmorpholine. [f]The reaction was performed with 5 mol % $Cu(CH_3CN)_4BF_4$ and 6 mol % **L12** in DCM (0.5 mL).

amino acids were also evaluated for their ability to promote this APS reaction (entries 2−7). In all cases, the desired products were obtained in yields comparable to that with **L1**. Interestingly, the highest enantioselectivity (83% ee) was obtained for ligand **L5** bearing less bulky methyl groups, although the diastereoselectivity was rather low (1.4:1) (entry 5). Indenylpybox ligand **L8** was not suitable for this reaction since no formation of **3aa** was observed (entry 8). Unexpectedly, installing a phenyl substituent at C5 of each oxazoline ring of the pybox ligand (**L9**) resulted in an enhanced reaction rate, allowing for complete conversion in 4 h (90% yield) along with a slight improvement (relative to **L5**) in enantioselectivity (entry 9). Further screening of pybox ligands with different substitution patterns revealed that **L12** was the best in terms of both yield and stereoselectivity (entries 10−16).

Attempts to improve the performance of the APS reaction by screening copper salts and solvents proved unsuccessful in that the initial results could not be improved further (data not shown; see the Supporting Information for details). Switching the base from DIPEA to *N*-ethylmorpholine (NEM) (entry 17) in the presence of **L12** led to a slight increase (relative to entry 12) in diastereoseclectivity (2.4:1 to 3.2:1) while providing almost identical yield and ee values. The reaction temperature was found to have a readily discernible impact on the diastereoselectivity. APS reactions carried out at −40 °C afforded a dr of 7.6:1 with 97% ee for the major diastereoisomer without affecting the high conversion, albeit at the expense of longer reaction times (entry 18). Further lowering the temperature to −50 °C gave a lower yield of 70% after 96 h. Reducing the loading of both components of the copper complex as well as the volume of the solvent by 50% still gave rise to an excellent yield of **3aa** without deterioration of either the dr or ee (entry 20).

With the optimized reaction conditions established (Table 1, entry 20), we chose α-phenyl nitroacetate **2a** as the model nucleophile to explore the reaction scope and assess the effect of different substituents at the propargylic position (Table 2).

Table 2. Scope of Terminal Alkyne Propargylic Carbonates[a]



1k: R = CH_3; **1l**: R = Bn
1m:R = Et; **1n**: R = Bu

entry	**1**, R	**3**	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**, C_6H_5	**3aa**	93	7.6:1	97
2	**1b**, 4-ClC_6H_4	**3ba**	83	4.2:1	96
3	**1c**, 4-FC_6H_4	**3ca**	84	5.7:1	97
4	**1d**, 4-BrC_6H_4	**3da**	80	5.5:1	96
5	**1e**, 4-MeC_6H_4	**3ea**	97	8.7:1	97
6	**1f**, 4-$MeOC_6H_4$	**3fa**	93	20:1	97
7	**1g**, 2-$MeOC_6H_4$	**3ga**	78	6:1	90
8	**1h**, 3-BrC_6H_4	**3ha**	78	5.3:1	96
9	**1i**, 1-naphthyl	**3ia**	83	1.5:1	91 (83)
10	**1j**, 2-thienyl	**3ja**	78	1.8:1	86 (82)
11	**1k**, CH_3	**3ka**	70	5.6:1	68
12	**1l**, Bn	**3la**	71	4.2:1	92
13	**1m**, Et	**3ma**	74	6.8:1	97
14	**1n**, Bu	**3na**	77	6.9:1	97

[a]General conditions: **1** (0.1 mmol), **2a** (0.2 mmol), Cu-$(CH_3CN)_4BF_4$ (5 mol %), ligand (6 mol %), and *N*-ethylmorpholine (2 equiv) in DCM (0.5 mL) at 40 °C for 48−72 h. [b]Yields of isolated pure **3**. [c]The dr of **3** was determined by ^{1}H NMR spectroscopy. [d]The ee's of the major diastereoisomers were determined by chiral HPLC analysis; values in parentheses are the ee's of the minor diastereoisomers.

To our delight, phenylpropargylic carbonate substrates bearing various electron-withdrawing or -donating substituents at the *para* position of the benzene ring (entries 1−6) all performed well and afforded phenylglycine derivatives **3aa**−**fa** in good to excellent yields (80−97%). Synthetically useful diastereoselectivities (4.2:1 to 20:1) and excellent enantioselectivities (96−97% ee) were also seen. Substrates bearing a substituent at the *ortho* or *meta* positions of the benzene ring were also examined; again, the corresponding products **3ga** and **3ha** were obtained readily (entries 7 and 8). The presence of a bulky 1-naphthyl group did not reduce the efficiency of the catalysis, although a lower diastereoselectivity was seen (entry

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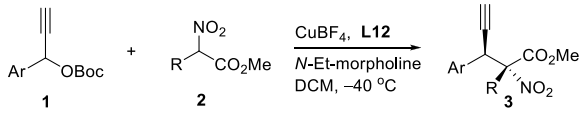
9). A notably lower enantioselectivity (86% ee) was observed for 2-thienyl-substituted substrate **1j** (entry 10). Alkyl-substituted precursors **1k**, **1m**, **1n** and benzyl-substituted precursor **1l**, which were prepared from the corresponding alcohols and perfluorobenzoic chloride, reacted smoothly with **2a** to afford the desired products in satisfactory fashion (entries 11−14), although a moderate level of enantioselectivity was seen in the case of **1k**. It is possible that the reduced steric demands of the methyl substituent in **1k** resulted in a less efficient chiral induction.

Next, the present study was extended to α-substituted nitroacetates (Table 3). We were pleased to find that

Table 3. Scope of α-Substituted Nitroacetates[a]



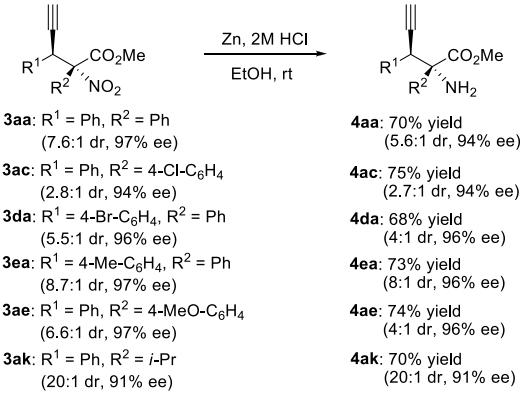
entry	1, 2, R	3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**, **2a**, C_6H_5	**3aa**	93	7.6:1	97
2	**1a**, **2b**, 4-FC_6H_4	**3ab**	82	4.7:1	96
3	**1a**, **2c**, 4-ClC_6H_4	**3ac**	75	2.8:1	94
4	**1a**, **2d**, 4-MeC_6H_4	**3ad**	92	6.2:1	96
5	**1a**, **2e**, 4-$MeOC_6H_4$	**3ae**	91	6.6:1	97
6	**1a**, **2f**, 3-$MeOC_6H_4$	**3af**	88	2.7:1	95 (78)
7	**1a**, **2g**, 2-$MeOC_6H_4$	**3ag**	84	4:1	90
8	**1a**, **2h**, 1-naphthyl	**3ah**	80	10:1	89
9	**1a**, **2i**, CH_3	**3ai**	86	1.6:1	88 (85)
10	**1a**, **2j**, CH_3CH_2	**3aj**	83	3.5:1	84
11	**1a**, **2k**, *i*-Pr	**3ak**	85	20:1	91
12	**1a**, **2l**, *n*-Bu	**3al**	94	3.6:1	89
13	**1a**, **2m**, Bn	**3am**	78	2:1	93 (85)
14	**1a**, **2n**, $MeO_2C(CH_2)$	**3an**	71	1.7:1	86 (79)
15	**1a**, **2o**, $MeO_2C(CH_2)_2$	**3ao**	88	1.9:1	84 (72)
16	**1d**, **2e**, 4-$MeOC_6H_4$	**3de**	75	3.6:1	93
17	**1d**, **2h**, 1-naphthyl	**3dh**	85	20:1	83
18	**1e**, **2e**, 4-$MeOC_6H_4$	**3ee**	84	6.3:1	95
19	**1e**, **2k**, *i*-Pr	**3ek**	88	15:1	97
20	**1f**, **2k**, *i*-Pr	**3fk**	80	20:1	90

[a]General conditions: **1** (0.1 mmol), **2** (0.2 mmol), $Cu(CH_3CN)_4BF_4$ (5 mol %), ligand (6 mol %), and *N*-ethylmorpholine (2 equiv) in DCM (0.5 mL) at 40 °C for 48−72 h. [b]Yields of isolated pure **3**. [c]The dr of **3** was determined by ^{1}H NMR spectroscopy. [d]The ee's of the major diastereoisomers were determined by chiral HPLC analysis; values in parentheses are the ee's of the minor diastereoisomers.

substrates **2b−g**, which are precursors to substituted phenylglycines, reacted with **1a** smoothly regardless of the electronic nature of the substituents. These reactions provided the desired propargylic products in good yields with moderate to good diastereoselectivities and excellent enantioselectivities (entries 2−7). A bulky naphthyl substituent was also tolerated in this reaction (entry 8). Moreover, aliphatically substituted nitroacetates appeared to be good nucleophiles in this process (entries 9−15). However, the diastereoselectivity was in general lower than that seen in the case of the aromatically substituted nitroacetates, with the isopropyl substituent being an exception; here a dr of 20:1 was seen (entry 11). A benzyl substituent was also compatible with the reaction, leading to **3am**, which is a precursor for α-substituted phenylalanines (entry 13). Side chains bearing an ester functional group were also tolerated (entries 14 and 15), and the propargylation products could be used to prepare α-substituted aspartic acid and glutamic acid, respectively. The scope was further expanded to *p*-bromophenyl (**1d**), *p*-methylphenyl (**1e**), and *p*-methoxyphenyl (**1f**) substituted propargylic carbonates (entries 16−20). Reactions between two alkyl partners, e.g., **1l** + **2k** and **1l** + **2j**, were also tested. Unfortunately, no formation of the propargylation product was observed.

The nitro ester products could be readily converted to α-amino carboxylic esters by reduction with zinc in aqueous HCl/EtOH at room temperature. As shown in Scheme 2, a

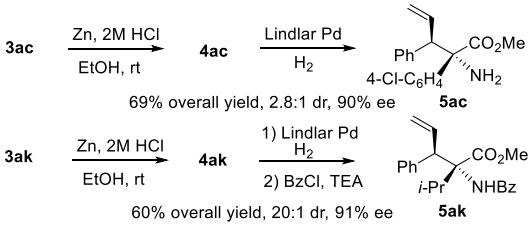
Scheme 2. Reduction of Nitro Esters over Zn/HCl



variety of propargylation adducts could be reduced to the corresponding amino carboxylic esters in good yields using this approach. Moreover, the enantioselectivities remained similar within experimental error for all of the compounds obtained in this way. On the other hand, a slight decrease in the diastereoselectivity was observed for most of the substrates, possibly because of epimerization at the propargylic position. Other reduction conditions, such as $NaBH_4/NiCl_2$ and Zn/AcOH, were also tested and found to be unsuitable for promoting this transformation.

The absolute stereochemistry of propargylation adduct **3ac** bearing an aromatic substituent at the α-position was determined to be 2*S*,3*R* by chemical correlation after its transformation to **5ac** through reduction with zinc followed by hydrogenation over Lindlar catalyst (Scheme 3).[9] Similarly, the

Scheme 3. Derivatization of 3ac and 3ak for Structural Elucidation



stereochemistry of **3ak** bearing an aliphatic substituent at the α-position was determined to be 2*R*,3*R*.[9] Furthermore, the absolute stereochemistry of **3ah** was determined to be 2*S*,3*R* by means of single-crystal X-ray diffraction analysis.[10] Stereochemical assignments for the other propargylation products were then assigned by making correlations to (2*S*,3*R*)-**3ac**, (2*S*,3*R*)-**3ah**, or (2*R*,3*R*)-**3ak** as appropriate.

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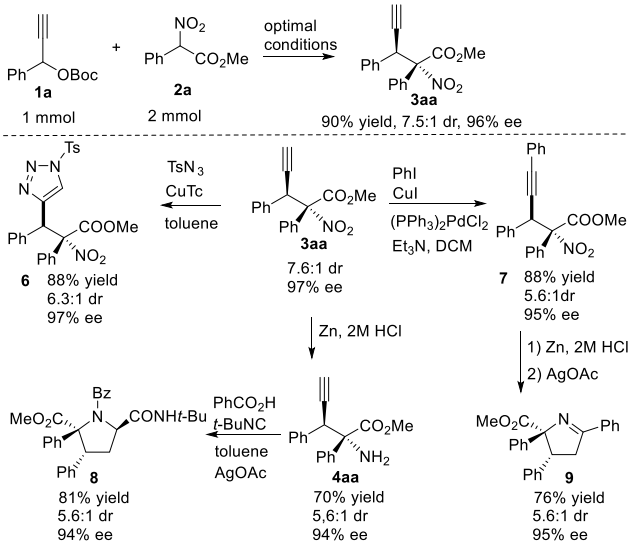
The practicality of the current method was further demonstrated by carrying out a relatively large scale synthesis of **3aa**. Specifically, under optimized conditions, the reaction between **1a** and **2a** was carried out on a 1 mmol scale; this gave the propargylation product **3aa** in 90% yield with a dr of 7.5:1 in 96% ee (Scheme 4). Standard postsynthetic functionalization of the terminal alkyne functionality of **3aa** was effected by means of (1) a click reaction with tosyl azide and (2) a Sonogashira reaction with phenyl iodide. Moreover, amino ester **4aa** could be elaborated into a densely substituted tetrahydropyrrole in an overall yield of 81% by adopting the protocol developed by Zhu et al.[11] Moreover, cyclic imine **9** could be obtained from coupling product **7** by reduction of the nitro group and subsequent intramolecular cyclization in the presence of AgOAc.

Scheme 4. Synthesis of 3aa on a 1 mmol Scale and Its Further Derivatization



In summary, we have developed a diastereo- and enantioselective propargylation reaction of α-substituted nitroacetates with various propargylic carbonates bearing a terminal alkyne moiety by employing a copper−pybox complex as the catalyst. A series of quaternary α-amino acid derivatives featuring adjacent tertiary and quaternary chiral centers along with a terminal alkyne moiety were obtained in high yields with good diastereoselectivities and excellent enantioselectivities in most cases. The use of pybox ligands bearing aryl substituents at the 5-positions of the oxazoline rings and *N*-ethylmorpholine as an added base proved vital to the success of this transformation. The nitro group of the propargylated adducts could be reduced to the corresponding amine functionality to give amino carboxylic esters. The utility of this methodology was further demonstrated by a carrying out a larger-scale synthesis of **3aa** and demonstrating that the resulting terminal alkyne and nitro moieties could be further elaborated using known chemistries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03894.

Experimental procedures and spectroscopic data for new compounds (PDF)

Accession Codes

CCDC 1949829 and 1960014 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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