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Enantioselective Copper-Catalyzed Decarboxylative Propargylic Alkylation of Propargylic Esters with β-Keto Acids

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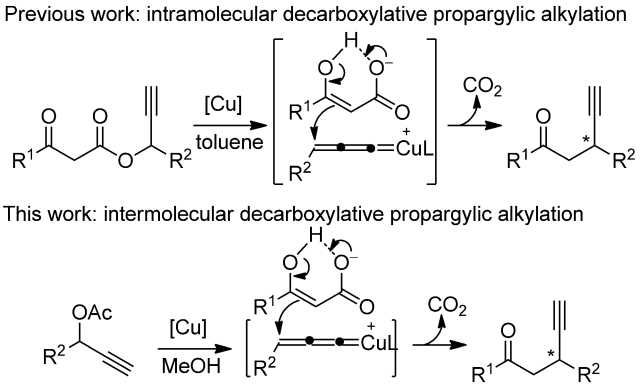
Abstract: The first copper-catalyzed intermolecular enantioselective decarboxylative propargylic alkylation of propargylic esters with β-keto acids as surrogates of ketones has been successfully developed by using a ketimine P,N,N-ligand. High yields and excellent enantioselectivities (up to 98% *ee*) have been achieved under the mild reaction conditions.

Keywords: asymmetric catalysis; copper; decarboxylative propargylic alkylation; β-keto acids; propargylic esters

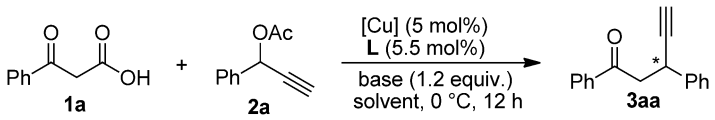


Scheme 1. Copper-catalyzed decarboxylative propargylic alkylation.

The catalytic asymmetric propargylic substitution of propargylic esters with various nucleophiles has been developed in the past decade.[1] However, the use of carbanions, especially unstabilized ketone enolates as nucleophiles, remains very limited.[2] Since the asymmetric alkylation of unstabilized ketone enolates constitutes one of the most powerful tools for constructing chiral centers *via* C–C bond forming reactions,[3] the development of a new strategy for the seteroselective propargylic alkylation of propargylic esters with unstabilized ketone enolates is particularly appealing.

Quite recently, we reported a strategy for the enantioselective propargylic alkylation of ketone enolates by a copper-catalyzed intramolecular decarboxylative alkylation of propargylic β-keto esters. The reaction works through the loss of CO_2 and does not need preformed ketone enloates.[4,5] The mechanistic study suggested that the reaction proceeded with a copper allenylidene complex enolate ion pair as the key intermediate (Scheme 1). We therefore envisioned that an intermolecular decarboxylative propargylic alkylation could also be possible since a similar ion pair could be generated when a propargylic ester and a β-keto acid were subjected to a copper catalyst under the appropriate reaction conditions (Scheme 1).[6] Although some examples have shown that β-keto acids are capable of undergoing the decarboxylative carbon-carbon bond-forming reaction as surrogates of ketones with various carbon electrophiles,[7] the decarboxylative alkylation with the use of a propargylic ester as the carbon electrophile remains unexplored. Herein, we report the first copper-catalyzed intermolecular asymmetric decarboxylative propargylic alkylation of propargylic esters with β-keto acids, in which excellent performance has been achieved. Importantly, this process provides an efficient way to obviate employing preformed propargylic β-keto esters for the intramolecular decarboxylation through the transesterification between the corresponding propargylic alcohols and β-keto esters, which generally requires long reaction time (up to 3 days) and gives unsatisfactory yields.

Table 1. Screening the reaction conditions.[a]



Entry	[Cu]	L	Base	Yield [%][b]	*ee* [%][c]
1[d]	$Cu(MeCN)_4BF_4$	**L1**	Et_3N	–	–[e]
2	$Cu(MeCN)_4BF_4$	**L1**	Et_3N	91	98 (*R*)
3	$Cu(MeCN)_4BF_4$	**L2**	Et_3N	90	93 (*S*)
4	$Cu(MeCN)_4BF_4$	**L3**	Et_3N	65	38 (*S*)
5	$Cu(MeCN)_4BF_4$	**L4**	Et_3N	–	–[e]
6	$Cu(MeCN)_4BF_4$	**L5**	Et_3N	90	13 (*S*)
7	$Cu(MeCN)_4BF_4$	**L1**	–	–	–[e]
8	$Cu(MeCN)_4BF_4$	**L1**	DBU	76	95 (*R*)
9	$Cu(MeCN)_4BF_4$	**L1**	$(i\text{-Pr})_2NEt$	88	96 (*R*)
10	CuI	**L1**	Et_3N	89	92 (*R*)
11	CuCl	**L1**	Et_3N	88	97 (*R*)
12	$Cu(OAc)_2{\cdot}H_2O$	**L1**	Et_3N	90	96 (*R*)

[a] *Reaction conditions:* **2a** (0.3 mmol), **1a** (0.33 mmol), [Cu] (0.015 mmol, 5 mol%), **L** (0.0165 mmol, 5.5 mol%), base (0.36 mmol), 3 mL of MeOH unless otherwise specified, 0 °C, 12 h.
[b] Isolated yield.
[c] The *ee* value was determined by chiral HPLC analysis.
[d] The reaction was performed in toluene.
[e] Not determined due to low conversion.

We started our investigation by examining the copper-catalyzed decarboxylative propargylic alkylation between benzoylacetic acid **1a** and 1-phenyl-2-propynyl acetate **2a** under the reaction conditions (Et_3N as the base, in toluene at 0 °C for 12 h) that had proved to be optimal in the corresponding intramolecular decarboxylative propargylic alkylation of propargylic β-keto esters.[4]

To our disappointment, however, no desired decarboxylative product was observed (Table 1, entry 1). The reason might be the low polarity of toluene, which prevented the approach of an enolate ion to the copper allenylidene complex. We therefore presumed that a strongly polar solvent such as MeOH should be a better choice for this reaction. The subsequent decarboxylative alkylation performed in MeOH confirmed our speculation, affording the desired β-ethynyl ketone **3aa** in high yield (91%) and with excellent enantioselectivity (98% *ee*) (entry 2). A remarkable ligand effect was observed. Chiral 1-phenylethylamine-derived tridentate P,N,N-ligands **L1** and **L2** (Figure 1) delivered excellent yields and *ee*s (entries 2 and 3). In contrast, BINAP (**L4**) led to very low conversion (entry 5). The addition of a base additive was necessary since none of β-ethynyl ketone **3aa** was obtained in its absence (entry 7). Other bases such DBU and $(i\text{-Pr})_2NEt$ also gave good results (entries 8 and 9). The Cu salt had less effect on the reactivity and enantioselectivity, and excellent performance was achieved with all Cu salts tested (entries 10–12).

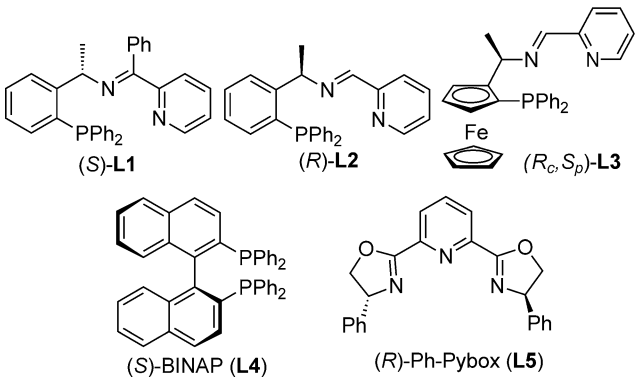


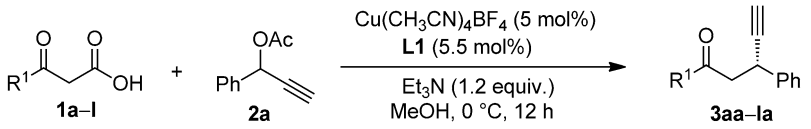
Figure 1. Ligands screened in Cu-catalyzed intermolecular decarboxylative propargylic alkylation.

Having identified the optimal reaction conditions for intermolecular decarboxylative propargylic alkylation, we next conducted the reactions of various β-keto acids with 1-phenyl-2-propynyl acetate (**2a**). The results in Table 2 disclosed that a wide range of aromatic β-keto acids smoothly underwent the decarboxylative alkylation with **2a**, providing the corresponding β-ethynyl ketones in high yields and with excellent enantioselectivities (entries 1–10). An exception was **1b** bearing a 2-Cl group, which gave only a moderate yield presumably due to the steric effect (entry 2). The reaction tolerated both electron-rich and electron-deficient aromatic groups, irrespective of whether the aromatic group was an aryl or a heteroaryl

group. However, in comparison with their aromatic counterparts, the reaction with aliphatic β-keto acids gave lower enantioselectivities (entries 11 and 12). In the case of 3-oxo-4-phenylbutanoic acid (**1l**), the product 1,4-diphenylhex-5-yn-2-one (**3la**) was obtained in 75% yield and with 87% *ee* (entry 12).

We next turned our attention to the decarboxylative alkylation of benzoylacetic acid (**1a**) with various propargylic acetates (**2**), and the results are summarized in Table 3. All aryl-substituted propargylic acetates underwent the reaction to give the corresponding products in high yields and with excellent enantioselectivity (entries 1–10). The position and electronic

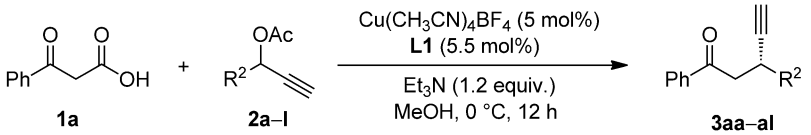
Table 2. Copper-catalyzed intermolecular decarboxylative propargylic alkylation: scope of β-keto acids.[a]



Entry	β-Keto acid (**1**)	Product (**3**)	Yield [%][b]	*ee* [%][c]
1	**1a**: R^1 = Ph	**3aa**	91	98 (*R*)
2	**1b**: R^1 = 2-ClC_6H_4	**3ba**	65	91 (*R*)
3	**1c**: R^1 = 3-ClC_6H_4	**3ca**	90	98 (*R*)
4	**1d**: R^1 = 4-ClC_6H_4	**3da**	88	98 (*R*)
5	**1e**: R^1 = 4-FC_6H_4	**3ea**	91	98 (*R*)
6	**1f**: R^1 = 4-BrC_6H_4	**3fa**	92	98 (*R*)
7	**1g**: R^1 = 4-MeC_6H_4	**3ga**	85	96 (*R*)
8	**1h**: R^1 = 2-naphthyl	**3ha**	76	97 (*R*)
9	**1i**: R^1 = 6-MeO-2-naphthyl	**3ia**	79	98 (*R*)
10	**1j**: R^1 = 2-thienyl	**3ja**	87	97 (*R*)
11	**1k**: R^1 = Me	**3ka**	65	74 (*R*)
12	**1l**: R^1 = Bn	**3la**	75	87 (*R*)

[a] *Reaction conditions:* **2a** (0.3 mmol), **1** (0.33 mmol), $Cu(MeCN)_4BF_4$ (0.015 mmol, 5 mol%), **L1** (0.0165 mmol, 5.5 mol%), Et_3N (0.36 mmol), 3 mL of MeOH, 0 °C, 12 h.
[b] Isolated yield.
[c] The *ee* value was determined by chiral HPLC analysis.

Table 3. Copper-catalyzed intermolecular decarboxylative propargylic alkylation: scope of propargylic acetates.[a]



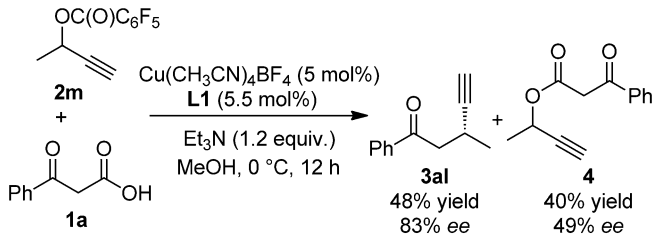
Entry	Propargylic acetate (**2**)	Product (**3**)	Yield [%][b]	*ee* [%][c]
1	**2a**: R^2 = Ph	**3aa**	91	98 (*R*)
2	**2b**: R^2 = 2-ClC_6H_4	**3ab**	80	96 (*R*)
3	**2c**: R^2 = 3-ClC_6H_4	**3ac**	91	97 (*R*)
4	**2d**: R^2 = 4-ClC_6H_4	**3ad**	87	97 (*R*)
5	**2e**: R^2 = 4-FC_6H_4	**3ae**	90	96 (*R*)
6	**2f**: R^2 = 4-BrC_6H_4	**3af**	93	97 (*R*)
7	**2g**: R^2 = 4-MeC_6H_4	**3ag**	84	94 (*R*)
8	**2h**: R^2 = 4-$MeOC_6H_4$	**3ah**	82	94 (*R*)
9	**2i**: R^2 = 4-$CF_3C_6H_4$	**3ai**	90	96 (*R*)
10	**2j**: R^2 = 2-naphthyl	**3aj**	84	95 (*R*)
11	**2k**: R^2 = 2-thienyl	**3ak**	89	93 (*R*)
12	**2l**: R^2 = Me	**3al**	–	–[d]

[a] *Reaction conditions:* **2** (0.3 mmol), **1a** (0.33 mmol), $Cu(MeCN)_4BF_4$ (0.015 mmol, 5 mol%), **L1** (0.0165 mmol, 5.5 mol%), Et_3N (0.36 mmol), 3 mL of MeOH, 0 °C, 12 h.
[b] Isolated yield.
[c] The *ee* value was determined by chiral HPLC analysis.
[d] Not determined due to low conversion.

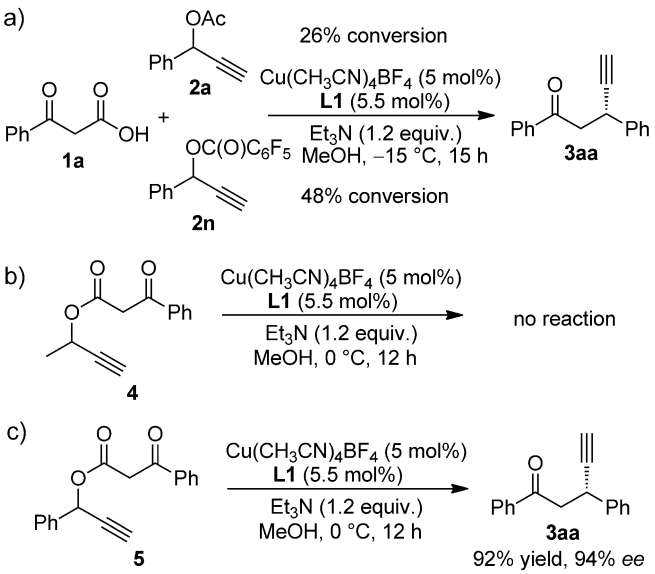
effect of the substituent on the benzene ring had little influence on the reactivity and enantioselectivity. The heteroaromatic substrate **2k** was also a suitable reaction partner for this reaction (entry 11). However, similar to what was observed in the Cu-catalyzed asymmetric propargylic substitution,[6] propargylic esters bearing an alkyl group at the propargylic position proved to be inefficient for this reaction (entry 12). No conversion was observed when but-3-yn-2-yl acetate (**2l**) was subjected to the reaction (entry 12).

Recently, Nishibayashi has reported that the introduction of a pentafluorobenzoate group instead of the acetate group into the propargylic ester could significantly promote the copper-catalyzed propargylic amination of aliphatic propargylic esters.[6] This strategy should also be suitable to the present decarboxylative alkylation. We prepared the pentafluorobenzoate (**2m**) of but-3-yn-2-ol, and subjected it to the decarboxylative alkylation under the optimized conditions (Scheme 2). As expected, the desired decarboxylative alkylation product **3al** was obtained in 48% yield and with 83% *ee*. This result suggested that the pentafluorobenzoxy group should be a better leaving group than the corresponding acetoxy group. To further confirm this observation, both 1-phenyl-2-propynyl acetate (**2a**) and pentafluorobenzoate (**2n**) were subjected to this reaction. Under the same reaction conditions, pentafluorobenzoate **2n** reacted more rapidly as expected (Scheme 3a).

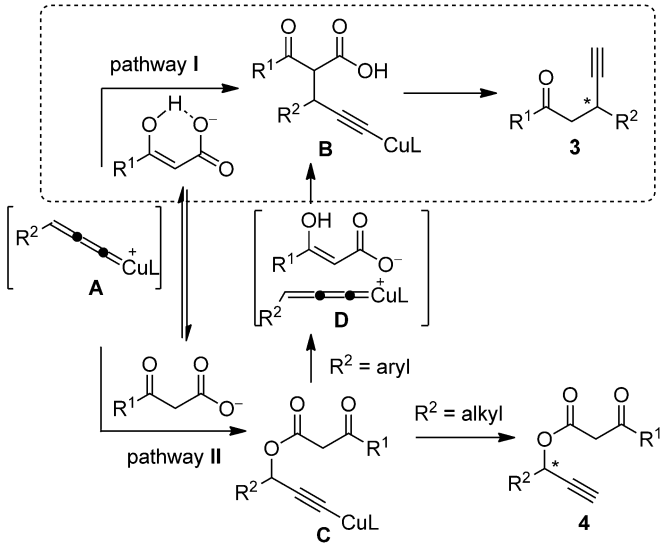
Besides **3al**, however, a substantial amount of transesterification product, but-3-yn-2-yl benzoylacetate **4**, was isolated as a side product (Scheme 2). This interesting observation suggested that a competitive reaction pathway, a transesterification process followed by an intramolecular decarboxylative alkylation, should be present as shown in the pathway **II** (Scheme 4). The formation of transesterification intermediate (**C**) from the attack of carboxylic oxygen at the C_γ atom of the copper allenylidene complex (**A**), might prevent the subsequent transformation since an aliphatic propargyl β-keto esters could not undergo the intramolecular decarboxylative propargylic alkylation as shown in Scheme 3b. This should be responsible for the low conversion of decarboxylative alkylation product **3al**. For aliphatic propargylic esters, the decarboxylative alkylation probably proceeded through pathway **I** in Scheme 4, in which the enolate carbanion attacked at the C_γ atom of the copper allenylidene complex (**A**) with the subsequent loss of CO_2 to give the desired decarboxylative alkylation product **3**. For aromatic propargylic esters, both reaction pathways are possible since aromatic propargylic β-keto esters also worked well under the same reaction conditions (Scheme 3c) as we had previously observed.[4] Further investigations to elucidate the reaction mechanism are underway.



Scheme 2. Cu-catalyzed asymmetric decarboxylative propargylic alkylation of but-3-yn-2-yl pentafluorobenzoate (**2m**) with benzoylacetic acid (**1a**).



Scheme 3. Mechanistic investigations into the copper-catalyzed decarboxylative propargylic alkylation.



Scheme 4. Proposed reaction mechanism.

In summary, we have developed the first intermolecular asymmetric decarboxylative propargylic alkylation of propargylic esters with β-keto acids as attractive surrogates of ketones. In the presence of 5 mol% of copper catalyst prepared *in situ* from $Cu(CH_3CN)_4BF_4$ and a tridentate chiral P,N,N-ligand, a variety of β-keto acids with propargylic esters underwent the decarboxylative propargylic alkylation to give the corresponding β-ethynyl ketones in good yields and with good to excellent *ee* (up to 98% *ee*).[8] In comparison to the corresponding intramolecular decarboxylative propargylic alkylation of propargylic β-keto esters, the present method displays some significant advantages: (i) more readily available substrates; (ii) generally better enantioselectivities; (iii) broader substrate scope (for example, aliphatic propargylic esters also worked). Furthermore, the present study suggested that two competitive reaction pathways should be present in the intermolecular decarboxylative propargylic alkylation. The further development and application of this reaction, as well as a study of the mechanism, is underway.

Experimental Section

General Procedure for Copper-Catalyzed Intermolecular Asymmetric Decarboxylative Propargylic Alkylation

$Cu(CH_3CN)_4BF_4$ (4.7 mg, 0.015 mmol) and (*S*)-**L1** (7.8 mg, 0.0165 mmol) were stirred at room temperature in 1 mL of anhydrous methanol under a nitrogen atmosphere for 1 h. The solution was then cooled to 0 °C, and a solution of β-keto acid (0.33 mmol), propargylic ester (0.3 mmol) and Et_3N (50 μL, 0.36 mmol) in 2 mL of anhydrous methanol was added. The mixture was stirred at 0 °C for 12 h. The reaction was quenched by 1 mL of a buffer of NaOAc/AcOH, and extracted with EtOAc (5 mL × 2). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was then purified by silica gel chromatography to afford the β-ethynyl ketone product.

(*R*)-1,3-Diphenylpent-4-yn-1-one (3aa): White solid; 91% yield; 98% *ee* was determined by chiral HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 70/30, 0.8 mL min^{-1}, 230 nm, 40 °C): t_R (minor) = 12.5 min, t_R (major) = 15.3 min; $[\alpha]_D^{25}$: −1.67 (*c* 0.46 g/100 mL, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.91 (m, 2H), 7.56–7.52 (m, 1H), 7.46–7.41 (m, 4H), 7.34–7.30 (m, 2H), 7.26–7.22 (m, 1H), 4.46–4.42 (m, 1H), 3.58 (dd, J_1 = 17.0 Hz, J_2 = 8.0 Hz, 1H), 3.34 (dd, J_1 = 17.0 Hz, J_2 = 6.0 Hz, 1H), 2.25 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 140.7, 136.8, 133.3, 128.7, 128.6, 128.2, 127.5, 127.2, 85.3, 71.1, 47.1, 32.7. The spectral data are in agreement with the reported values.[4]

Acknowledgements

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