

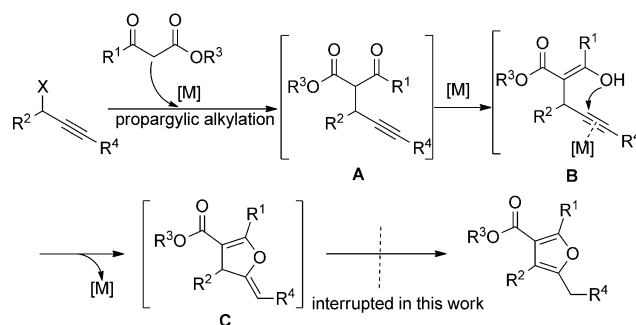
Enantioselective Synthesis of Highly Functionalized Dihydrofurans through Copper-Catalyzed Asymmetric Formal [3+2] Cycloaddition of β -Ketoesters with Propargylic Esters**

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Abstract: An enantioselective synthesis of highly functionalized dihydrofurans through a copper-catalyzed asymmetric [3+2] cycloaddition of β -ketoesters with propargylic esters has been developed. With a combination of $\text{Cu}(\text{OTf})_2$ and a chiral tridentate P,N,N ligand as the catalyst, a variety of 2,3-dihydrofurans bearing an exocyclic double bond at the 2 position were obtained in good chemical yields and with good to high enantioselectivities. The exocyclic double bond can be hydrogenated in a highly diastereoselective fashion to give unusual *cis*-2,3-dihydrofuran derivatives, thus further enhancing the scope of this transformation.

Dihydrofurans are common motifs in many natural products and pharmaceuticals, and also serve as attractive precursors in an array of organic transformations.^[1] Although many strategies have been described for the synthesis of various dihydrofurans,^[2] catalytic asymmetric approaches to access optically active 2,3-dihydrofurans are very limited and most rely on metal-catalyzed cycloadditions of diazo compounds with vinyl ether or enones and organocatalytic modified Feist-Bénary reactions.^[3] In particular, no catalytic asymmetric process for the synthesis of chiral 2,3-dihydrofurans bearing an exocyclic C=C bond at the 2 or 3 position has been developed. Therefore, the exploration of a new catalytic enantioselective method for the facile synthesis of chiral multifunctionalized 2,3-dihydrofurans is still in high demand.

In the past decade, catalytic sequential propargylation/cycloisomerization reactions of propargylic alcohols or their derivatives with 1,3-dicarbonyl compounds have been reported for the synthesis of substituted furans (Scheme 1).^[4] In these reactions, 2-alkylene-2,3-dihydrofurans (**C**) were proposed as the key intermediates for the subsequent isomerization to substituted furans. It was therefore anticipated that these reaction protocols should provide a concise access to 2-alkylene-2,3-dihydrofurans (**C**) if the last isomerization step can be efficiently interrupted. Indeed, an



Scheme 1. “Interrupted” catalytic propargylation/cycloisomerization for the synthesis of 2-alkylene-2,3-dihydrofurans.

intramolecular cyclization of 2-propynyl-1,3-dicarbonyl compounds (**A**, $\text{R}^2 = \text{H}$) catalyzed by a Cu-based system has been realized recently to form 2-alkylene-2,3-dihydrofurans.^[5] Combined with the recent success in the Cu-catalyzed asymmetric propargylic substitution,^[6] we therefore envisioned that the development of an enantioselective variant of this reaction should be feasible to produce chiral 2,3-dihydrofurans bearing an exocyclic C=C bond at the 2-position. Herein, we report the first examples of highly enantioselective Cu-catalyzed formal [3+2] cycloadditions of β -ketoesters with propargylic esters, employing a tridentate chiral P,N,N ligand and leading to optically active 2-methylene-2,3-dihydrofurans. More importantly, the exocyclic methylene C=C bond can be hydrogenated in a highly diastereoselective fashion to give unusual *cis*-2,3-dihydrofuran derivatives, in contrast to the *trans* diastereoisomers that are generated predominantly in other catalytic asymmetric processes reported so far.^[3]

Our preliminary studies focused on probing the effects of different ligands, copper salts, bases, and solvents on the efficiency and selectivity of the reaction. Having chosen methyl 3-oxo-3-phenylpropanoate (**1a**) and 1-phenylprop-2-yn-1-yl acetate (**2a**) as standard reaction partners, several chiral ligands that proved to be efficient in the Cu-catalyzed asymmetric propargylic substitution were investigated at the outset of our studies (Table 1, entries 1–6). Substituted furan **5** was not detected by ^1H NMR spectroscopy in any of the cases. However, the structure of the ligand showed a significant influence on the reactivity, chemoselectivity, and enantioselectivity of the reaction. With (*S*)-BINAP (**L1**) as the ligand, no reaction was observed (Table 1, entry 1). The use of Ph-pybox (**L2**) predominately gave the propargylic alkylation product **4** (Table 1, entry 2). When bis(oxazoline) **L3** was used as the ligand, the desired 2-methylene-2,3-dihydrofuran (**3aa**) was obtained as the main product, but with low enantiose-

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[**] Support for this research from the Dalian Institute of Chemical Physics (CAS) is gratefully acknowledged.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201405857>.

Table 1: Optimization of the copper-catalyzed asymmetric [3+2] cycloaddition of methyl 3-oxo-3-phenylpropanoate (**1a**) with 1-phenylprop-2-yn-1-yl acetate (**2a**).^[a]

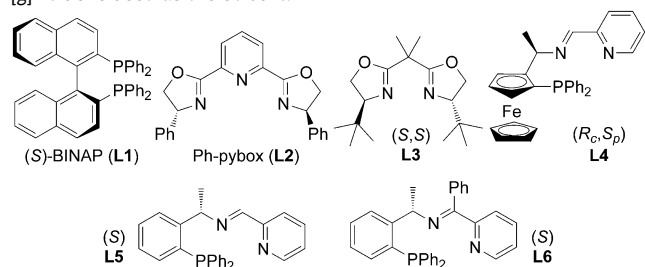
Entry	[Cu]	L*	Base	3 aa/4 ^[b]	3 aa Yield [%] ^[c]	ee [%] ^[d]
1	Cu(OAc) ₂ ·H ₂ O	L1	Et ₃ N	—	—	— ^[e]
2	Cu(OAc) ₂ ·H ₂ O	L2	Et ₃ N	< 5/95	—	— ^[e]
3	Cu(OAc) ₂ ·H ₂ O	L3	Et ₃ N	75/25	55	< 5
4	Cu(OAc) ₂ ·H ₂ O	L4	Et ₃ N	> 95/5	85	−39
5	Cu(OAc) ₂ ·H ₂ O	L5	Et ₃ N	> 95/5	84	43
6	Cu(OAc) ₂ ·H ₂ O	L6	Et ₃ N	> 95/5	88	92
7	CuI	L6	Et ₃ N	> 95/5	91	86
8	Cu(OTf) ₂	L6	Et ₃ N	> 95/5	90	95
9	Cu(OTf) ₂	L6	none	—	—	— ^[e]
10	Cu(OTf) ₂	L6	<i>i</i> Pr ₂ NEt	71/29	45	92
11 ^[f]	Cu(OTf) ₂	L6	Et ₃ N	—	—	— ^[e]
12 ^[g]	Cu(OTf) ₂	L6	Et ₃ N	—	—	— ^[e]

[a] Reaction conditions: **1a** (0.33 mmol), **2a** (0.3 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, room temperature, 15 h.

[b] Determined by ¹H NMR spectroscopy. [c] Yields of isolated products.

[d] Determined by HPLC analysis using a chiral stationary phase. [e] Not determined because of low conversion. [f] CH₂Cl₂ used as the solvent.

[g] Toluene used as the solvent.



lectivity (Table 1, entry 3). Subsequent ligand screening identified chiral tridentate P,N,N ligands^[6p,q,s-u] developed within our group as promising ligands (Table 1, entries 4–6). Among them, the bulky and structurally rigid ketimine-type P,N,N ligand **L6**,^[6s-u] which we developed very recently^[6u] for the Cu-catalyzed asymmetric decarboxylative propargylic alkylation, proved to be optimal, affording the desired 2-methylene-2,3-dihydrofuran **3aa** as the only product in good yield (88%) and with high enantioselectivity (92% *ee*; Table 1, entry 6). The screening of copper salts showed that Cu(OTf)₂ was the best choice, giving **3aa** as the only product in 90% yield and with an *ee* value of 95% (Table 1, entry 8). The base additive proved to be crucial. No reaction was observed in its absence, while the use of *i*Pr₂NEt in place of Et₃N as a base resulted in a detrimental effect on the chemoselectivity (Table 1, entries 9 and 10). Of the solvents that were tested, MeOH was the only suitable one, and no reaction occurred in CH₂Cl₂ or toluene (Table 1, entries 11

and 12). This result is consistent with those observed for the copper-catalyzed asymmetric propargylic substitution.^[6]

With optimized conditions in hand, the scope of the reaction with respect to β-ketoesters was explored (Table 2). The electronic properties of the substituent at the *para*

Table 2: Copper-catalyzed asymmetric [3+2] cycloaddition of β-ketoesters **1** with **2a**.^[a]

Entry	1 (R ¹)	Product	Yield [%] ^[b]	ee [%] ^[c]
1	1a (Ph)	3aa	90	95
2	1b (4-MeC ₆ H ₄)	3ba	83	97
3	1c (4-MeOC ₆ H ₄)	3ca	81	96
4	1d (4-FC ₆ H ₄)	3da	80	94
5	1e (4-BrC ₆ H ₄)	3ea	85	93
6	1f (4-ClC ₆ H ₄)	3fa	86	95
7	1g (3-ClC ₆ H ₄)	3ga	92	95
8 ^[d]	1h (2-ClC ₆ H ₄)	3ha	89	91
9	1i (2-naphthyl)	3ia	84	97
10	1j (2-thienyl)	3ja	88	97
11	1k (Me)	3ka	90	87
12	1l (Bn)	3la	89	87

[a] Reaction conditions: **1** (0.33 mmol), **2a** (0.3 mmol), Cu(OTf)₂ (0.015 mmol, 5 mol %), (S)-**L6** (0.0165 mmol, 5.5 mol %), Et₃N (0.36 mmol, 1.2 equiv), 3 mL of MeOH, room temperature, 15 h.

[b] Yields of isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 1-Phenylprop-2-yn-1-yl benzoate was used instead of acetate **2a**, as very low conversions (< 5%) were observed with acetate **2a**.

position of the phenyl ring had little effect on the reaction performance, and β-ketoesters bearing either electron-donating (Me, OMe) or electron-withdrawing (F, Br, and Cl) groups gave remarkably high yields and enantioselectivities (Table 2, entries 2–6). However, the reaction was highly sensitive to the substitution pattern on the phenyl ring. Thus, both 4-Cl- or 3-Cl-substituted substrates (**1f** or **1g**, respectively) gave the products in good yields and high enantioselectivities (Table 2, entries 6 and 7), while substrate **1h** bearing a 2-Cl substituent resulted in a very low conversion. When a benzoate of 1-phenylprop-2-yn-1-ol was used instead of the corresponding acetate **2a**, the reaction proceeded smoothly and gave the desired product **3ha** in 89% yield and with an *ee* value of 91% (Table 2, entry 8). 2-Naphthyl-substituted substrate **1i** also worked well, giving cycloadduct **3ia** in 84% yield and with 97% *ee* (Table 2, entry 9). Heteroaromatic substrate **1j** turned out to be a suitable reaction partner, providing cycloadduct **3ja** in 88% yield and with 97% *ee* (Table 2, entry 10). Remarkably, β-ketoesters with nonaromatic substituents were also well tolerated in this process, providing the corresponding cycloadducts **3ka** and **3la** in high yields, but with a slight decrease in enantioselectivities (both with 87% *ee*; Table 2, entries 11 and 12). The absolute configuration of 2-methylene-2,3-dihydrofurans was unambiguously determined by X-ray structure analysis of **3ea**, to which an *R* configuration was assigned (Figure 1).^[7]

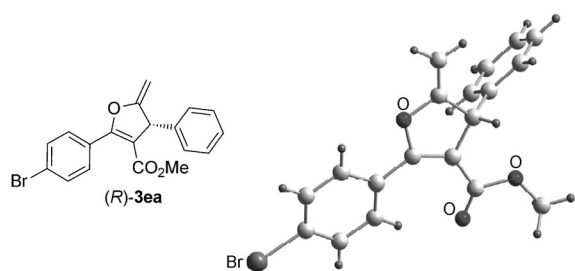


Figure 1. X-ray crystal structure of (R)-3ea.

After investigating the scope of β -ketoesters, we next examined the scope of propargylic esters (Table 3). Good performance was observed for aryl propargylic esters with both electron-donating and electron-withdrawing groups at

Table 3: Copper-catalyzed asymmetric [3+2] cycloaddition of **1a** with propargylic esters **2**.^[a]

Entry	2 (R^2)	Product	Yield [%] ^[b]	ee [%] ^[c]
1	2a (Ph)	3aa	90	95
2	2b (4-MeC ₆ H ₄)	3ab	88	93
3	2c (4-MeOC ₆ H ₄)	3ac	82	85
4	2d (4-CF ₃ C ₆ H ₄)	3ad	89	96
5	2e (4-FC ₆ H ₄)	3ae	90	96
6	2f (4-BrC ₆ H ₄)	3af	91	95
7	2g (4-ClC ₆ H ₄)	3ag	86	95
8	2h (3-ClC ₆ H ₄)	3ah	91	97
9	2i (2-ClC ₆ H ₄)	3ai	64	90
10	2j (2-naphthyl)	3aj	88	92
11	2k (2-thienyl)	3ak	87	84
12	2l (Me)	3al	< 5	–
13 ^[d]	2l' (Me)	3al	71	83
14 ^[d]	2m' (<i>n</i> -Pr)	3am	78	94
15 ^[d]	2n' (cyclohexyl)	3an	65	91 ^[e]

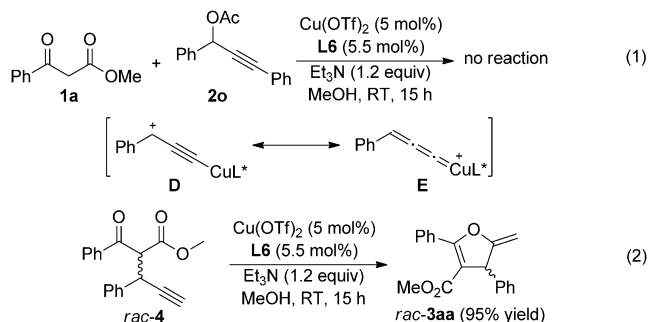
[a] Reaction conditions: **1a** (0.33 mmol), **2** (0.3 mmol), Cu(OTf)₂ (0.015 mmol, 5 mol %), (*S*)-**L6** (0.0165 mmol, 5.5 mol %), Et₃N (0.36 mmol, 1.2 equiv), 3 mL of MeOH, room temperature, 15 h.

[b] Yields of isolated products. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The pentafluorobenzoate was used instead of the corresponding acetate. [e] The reaction was performed for 24 h.

the *para* position (Table 3, entries 2–7). Increased steric bulk (**2i**) was tolerated, but led to somewhat diminished conversions (Table 3, entry 9). 2-Naphthyl (**2j**) and 2-thienyl (**2k**) substrates also served well in this reaction and gave the corresponding cycloadducts **3aj** and **3ak** with good results (Table 3, entries 10 and 11). The reaction also tolerated aliphatic substrates. In these cases, the pentafluorobenzoates **2l'–n'** should be used instead of the corresponding acetates in order to achieve good yields and enantioselectivities (Table 3, entries 13–15), as pentafluorobenzoate represents a better leaving group for aliphatic substrates, as reported by Nishibayashi.^[6n] Thus, the reaction of but-3-yn-2-yl pentafluorobenzoate (**2l'**) with β -ketoester **1a** gave cycloadduct **3al** in

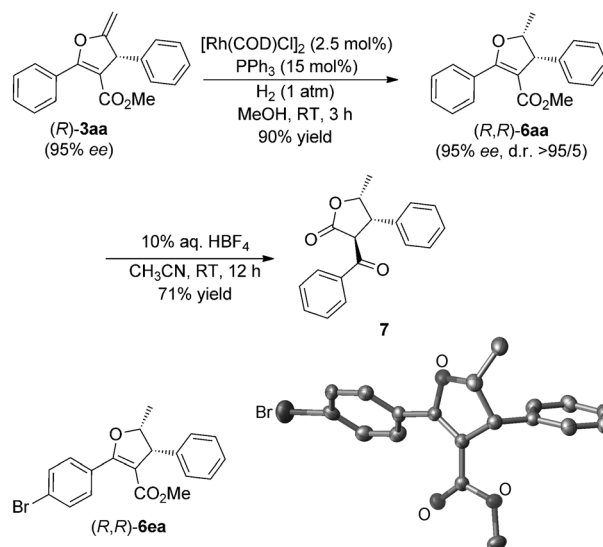
71 % yield with 83 % ee (Table 3, entry 13). In sharp contrast, very low conversion (< 5 %) was observed when but-3-yn-2-yl acetate **2l** was used as the substrate (Table 3, entry 12).

When an internal alkyne, 1,3-diphenyl-2-propynyl acetate (**2o**), was employed, no reaction occurred at all [Eq. (1)]. The necessity for the terminal acetylenic hydrogen atom means that the copper–acetylide complex (**D**), which features



a cationic γ -carbon atom or its resonance structure, the copper–allenylidene complex (**E**), should be generated in the initial step, as those observed with the Cu-catalyzed asymmetric propargylic substitution.^[6g,l] When an achiral intermediate **4** was subjected to this transformation, the reaction proceeded smoothly, but gave the cycloadduct **3aa** as a racemate [Eq. (2)]. This result suggested that the enantioselectivity of this reaction should not be affected by the cyclization step, but rather determined by the propargylic alkylation step.

In order to investigate the utility of our method for the generation of useful chiral building blocks, we carried out the hydrogenation of the exocyclic C=C bond of compound **3aa** (Scheme 2). The exocyclic methylene group could be readily hydrogenated in a highly diastereoselective fashion (d.r. > 95/5) without a loss in enantioselectivity through the catalysis by a combination of [Rh(COD)Cl]₂ and PPh₃, predominantly



Scheme 2. Stereoselective transformation of (R)-2-methylene-2,3-dihydrofuran derivatives.

giving the *cis* diastereoisomer in high yield. This result is unusual, as catalytic asymmetric approaches for the synthesis of chiral 2,3-dihydrofurans reported so far produced *trans* diastereoisomers as the major product. The absolute configuration of the *cis* diastereoisomer was unambiguously confirmed by X-ray structure analysis of **6ea**, to which an *R,R* configuration was assigned.^[7] The resulting (*R,R*)-**6aa** could be easily converted into the corresponding optically active γ -lactone **7** by the treatment with aqueous HBF₄ at room temperature (Scheme 2). The configuration of the new stereocenter in **7** was established on the basis of the NOE experiment.^[8]

In conclusion, we reported the copper-catalyzed asymmetric formal [3+2] cycloaddition of β -ketoesters with propargylic esters to generate optically active 2,3-dihydrofurans bearing an exocyclic C=C bond in high yield and enantioselectivity. A bulky and structurally rigid chiral ketimine-type P,N,N ligand was critical to achieve good performance. Under the optimized conditions, a range of substitution patterns at the β -ketoesters and propargylic esters were well tolerated. Rh-catalyzed hydrogenation of the cycloadducts, 2-methylene-2,3-dihydrofurans, resulted in the predominate formation of unusual *cis* diastereoisomer, which could be further transformed into the corresponding optically active γ -lactones. This demonstrates the value of this method for the generation of highly functionalized chiral building blocks. The further development and application of this reaction are underway.

Experimental Section

General procedure: A solution of Cu(OTf)₂ (5.4 mg, 0.015 mmol) and **L6** (7.8 mg, 0.0165 mmol) in anhydrous methanol (1 mL) was placed in an oven-dried Schlenk flask and stirred at room temperature under a nitrogen atmosphere for 1 h. A solution of β -ketoesters **1** (0.33 mmol), propargylic esters **2** (0.3 mmol), and Et₃N (50 μ L, 0.36 mmol) in anhydrous methanol (2 mL) was added. The mixture was stirred at room temperature for 15 h. The reaction mixture was then concentrated under vacuum, and the residue was purified by column chromatography on silica gel to afford the corresponding 2,3-dihydrofuran products **3**.

Received: June 2, 2014

Revised: July 17, 2014

Published online: August 1, 2014

Keywords: 2,3-dihydrofurans · asymmetric catalysis · copper · cycloadditions · synthetic methods

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- [8] For details of NOESY spectra for compound **7**, see the Supporting Information.