Asymmetric Catalysis

DOI: 10.1002/anie.201405857

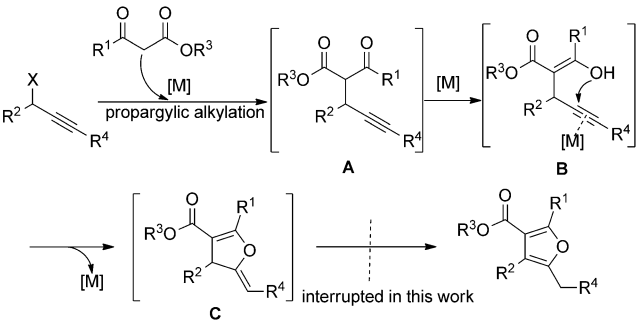
Enantioselective Synthesis of Highly Functionalized Dihydrofurans through Copper-Catalyzed Asymmetric Formal [3+2] Cycloaddition of β-Ketoesters with Propargylic Esters**

*Fu-Lin Zhu, Ya-Hui Wang, De-Yang Zhang, Jie Xu, and Xiang-Ping Hu**

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 $Cu(OTf)_2$ 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–Bènary 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 intramolecular cyclization of 2-propynyl-1,3-dicarbonyl compounds (**A**, $R^2 = H$) 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]



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

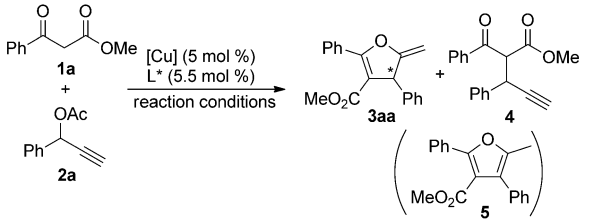
Our preliminary studies focused on probing the effects of different ligands, copper salts, bases, and solvents on the efficiency and selectivity of the reaction. Having chosen methyl 3-oxo-3-phenylpropanoate (**1a**) and 1-phenylprop-2-yn-1-yl acetate (**2a**) as standard reaction partners, several chiral 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-

[*] F.-L. Zhu, Y.-H. Wang, D.-Y. Zhang, Prof. Dr. J. Xu, Prof. Dr. X.-P. Hu
Dalian Institute of Chemical Physics
Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (China)
E-mail: xiangping@dicp.ac.cn
Homepage: http://www.asym.dicp.ac.cn
F.-L. Zhu, D.-Y. Zhang
University of Chinese Academy of Sciences
Beijing 100049 (China)

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

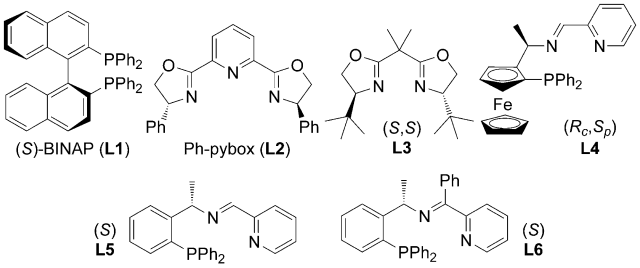
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405857.

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	**3aa**/**4**[b]	**3aa** Yield [%][c]	*ee* [%][d]
1	$Cu(OAc)_2{\cdot}H_2O$	**L1**	Et_3N	–	–	–[e]
2	$Cu(OAc)_2{\cdot}H_2O$	**L2**	Et_3N	<5/95	–	–[e]
3	$Cu(OAc)_2{\cdot}H_2O$	**L3**	Et_3N	75/25	55	<5
4	$Cu(OAc)_2{\cdot}H_2O$	**L4**	Et_3N	>95/5	85	−39
5	$Cu(OAc)_2{\cdot}H_2O$	**L5**	Et_3N	>95/5	84	43
6	$Cu(OAc)_2{\cdot}H_2O$	**L6**	Et_3N	>95/5	88	92
7	CuI	**L6**	Et_3N	>95/5	91	86
8	$Cu(OTf)_2$	**L6**	Et_3N	>95/5	90	95
9	$Cu(OTf)_2$	**L6**	none	–	–	–[e]
10	$Cu(OTf)_2$	**L6**	iPr_2NEt	71/29	45	92
11[f]	$Cu(OTf)_2$	**L6**	Et_3N	–	–	–[e]
12[g]	$Cu(OTf)_2$	**L6**	Et_3N	–	–	–[e]

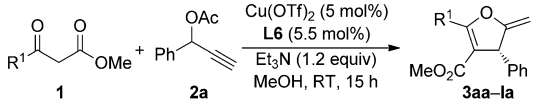
[a] Reaction conditions: **1a** (0.33 mmol), **2a** (0.3 mmol), [Cu] (0.015 mmol, 5 mol%), L* (0.0165 mmol, 5.5 mol%), base (0.36 mmol), 3 mL of MeOH unless otherwise specified, room temperature, 15 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Yields of isolated products. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Not determined because of low conversion. [f] CH_2Cl_2 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 iPr_2NEt in place of Et_3N 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 CH_2Cl_2 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* 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]

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_6H_4)	**3ba**	83	97
3	**1c** (4-$MeOC_6H_4$)	**3ca**	81	96
4	**1d** (4-FC_6H_4)	**3da**	80	94
5	**1e** (4-BrC_6H_4)	**3ea**	85	93
6	**1f** (4-ClC_6H_4)	**3fa**	86	95
7	**1g** (3-ClC_6H_4)	**3ga**	92	95
8[d]	**1h** (2-ClC_6H_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%), Et_3N (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**.

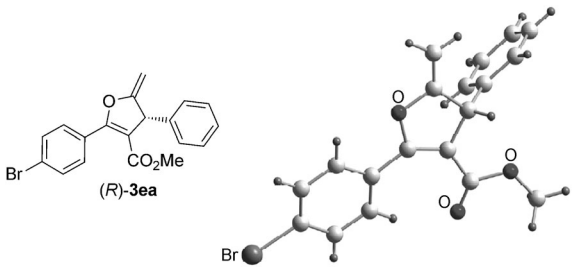
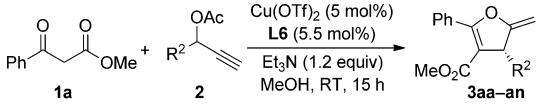


Figure 1. X-ray crystal structure of (*R*)-**3ea**.

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 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).

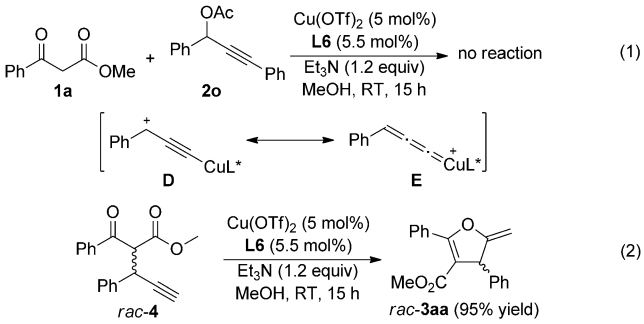
Table 3: Copper-catalyzed asymmetric [3+2] cycloaddition of **1a** with propargylic esters **2**.[a]



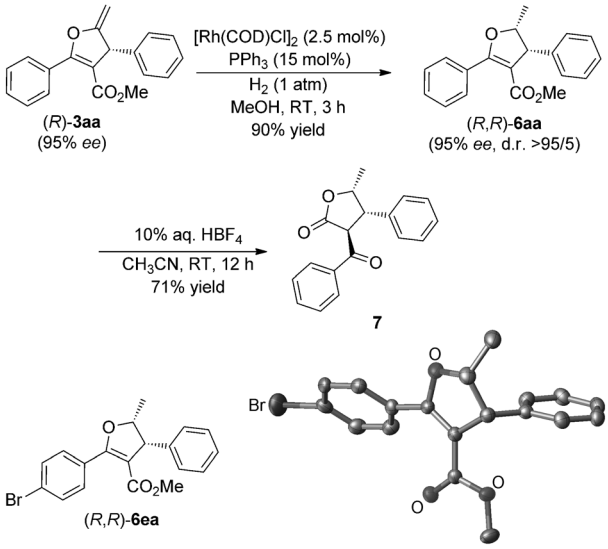
Entry	**2** (R^2)	Product	Yield [%][b]	*ee* [%][c]
1	**2a** (Ph)	**3aa**	90	95
2	**2b** (4-MeC_6H_4)	**3ab**	88	93
3	**2c** (4-$MeOC_6H_4$)	**3ac**	82	85
4	**2d** (4-$CF_3C_6H_4$)	**3ad**	89	96
5	**2e** (4-FC_6H_4)	**3ae**	90	96
6	**2f** (4-BrC_6H_4)	**3af**	91	95
7	**2g** (4-ClC_6H_4)	**3ag**	86	95
8	**2h** (3-ClC_6H_4)	**3ah**	91	97
9	**2i** (2-ClC_6H_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′** (*n*-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%), Et_3N (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.

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 PPh_3, 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 HBF_4 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-hydrofurans 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 Et_3N (50 μL, 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: ■■ ■■, ■■■■

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

[1] a) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795 – 819; b) B. M. Fraga, *Nat. Prod. Rep.* **1992**, *9*, 217 – 241; c) A. T. Merritt, S. B. Ley, *Nat. Prod. Rep.* **1992**, *9*, 243 – 287; d) M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407 – 2474; e) M. C. Elliott, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2301 – 2323; f) F. Garzino, A. Méou, P. Brun, *Synthesis* **2003**, 598 – 602; g) X.-L. Hou, Z. Yang, K.-S. Yeung, H. N. C. Wong, *Prog. Heterocycl. Chem.* **2005**, *17*, 142 – 171; h) T. G. Kilroy, T. P. O'Sullivan, P. J. Guiry, *Eur. J. Org. Chem.* **2005**, 4929 – 4949; i) J. D. Pettigrew, P. D. Wilson, *Org. Lett.* **2006**, *8*, 1427 – 1429.

[2] For selected examples, see: a) M. Aso, A. Ojida, G. Yang, O. J. Cha, E. Osawa, K. Kanematsu, *J. Org. Chem.* **1993**, *58*, 3960 – 3968; b) F. E. McDonald, C. B. Connolly, M. M. Gleason, T. B. Towne, K. D. Treiber, *J. Org. Chem.* **1993**, *58*, 6952 – 6953; c) S. C. Roy, P. K. Mandal, *Tetrahedron* **1996**, *52*, 2193 – 2198; d) M. Hamaguchi, H. Matsubara, T. Nagai, *Tetrahedron Lett.* **2000**, *41*, 1457 – 1460; e) G. Bar, A. F. Parsons, C. B. Thomas, *Tetrahedron Lett.* **2000**, *41*, 7751 – 7755; f) F. Garzino, A. Méou, P. Brun, *Tetrahedron Lett.* **2000**, *41*, 9803 – 9807; g) R. Antonioletti, G. Righi, L. Oliveri, P. Bovicelli, *Tetrahedron Lett.* **2000**, *41*, 10127 – 10130; h) Y. R. Lee, B. S. Kim, D. H. Kim, *Tetrahedron* **2000**, *56*, 8845 – 8853; i) Y. Wang, S. Zhu, *Tetrahedron* **2001**, *57*, 3383 – 3387; j) V. K. Yadav, R. Balamurugan, *Org. Lett.* **2001**, *3*, 2717 – 2719; k) Y. Zhang, A. J. Raines, R. A. Flowers II, *Org. Lett.* **2003**, *5*, 2363 – 2365; l) V. Calò, F. Scordari, A. Nacci, E. Schingaro, L. D'Accolti, A. Monopoli, *J. Org. Chem.* **2003**, *68*, 4406 – 4409; m) F. Garzino, A. Méou, P. Brun, *Eur. J. Org. Chem.* **2003**, 1410 – 1414; n) C. Xing, S. Zhu, *J. Org. Chem.* **2004**, *69*, 6486 – 6488; o) H. J. Gais, L. R. Reddy, G. S. Babu, G. Raabe, *J. Am. Chem. Soc.* **2004**, *126*, 4859 – 4864; p) R. Caliskan, T. Pekel, W. H. Watson, M. Balci, *Tetrahedron Lett.* **2005**, *46*, 6227 – 6230; q) W. Xia, C. Yang, B. O. Patrick, J. R. Scheffer, C. Scott, *J. Am. Chem. Soc.* **2005**, *127*, 2725 – 2730; r) A. M. Bernard, A. Frongia, P. P. Piras, F. Secci, M. Spiga, *Org. Lett.* **2005**, *7*, 4565 – 4568; s) R. K. Bowman, J. S. Jonhson, *Org. Lett.* **2006**, *8*, 573 – 576; t) J.-C. Zheng, C.-Y. Zhu, X.-L. Sun, Y. Tang, L.-X. Dai, *J. Org. Chem.* **2008**, *73*, 6909 – 6912; u) R. Zhang, Y. Liang, G. Zhou, K. Wang, D. Dong, *J. Org. Chem.* **2008**, *73*, 8089 – 8092; v) Z. Chen, J. Zhang, *Chem. Asian J.* **2010**, *5*, 1542 – 1545; w) M. Li, S. Lin, Z. Dong, X. Zhang, F. Liang, J. Zhang, *Org. Lett.* **2013**, *15*, 3978 – 3981; x) L. Xia, Y. R. Lee, *Adv. Synth. Catal.* **2013**, *355*, 2361 – 2374.

[3] For catalytic asymmetric cycloaddition of diazo compounds to form chiral 2,3-dihydrofurans, see: a) H. M. L. Davies, G. Ahmed, R. L. Calvo, M. R. Churchill, *J. Org. Chem.* **1998**, *63*, 2641 – 2645; b) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, S. Grass, *Synlett* **2005**, 1397 – 1400; c) S. Son, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 1046 – 1047; d) J.-L. Zhou, L.-J. Wang, H. Xu, X.-L. Sun, Y. Tang, *ACS Catal.* **2013**, *3*, 685 – 688. For organocatalytic Feist-Bènary reactions to form chiral 2,3-dihydrofurans, see: e) M. A. Calter, R. M. Phillips, C. Flaschenriem, *J. Am. Chem. Soc.* **2005**, *127*, 14566 – 14567; f) M. Rueping, A. Parra, U. Uria, F. Besselièvre, E. Merino, *Org. Lett.* **2010**, *12*, 5680 – 5683; g) L.-P. Fan, P. Li, X.-S. Li, D.-C. Xu, M.-M. Ge, W.-D. Zhu, J.-W. Xie, *J. Org. Chem.* **2010**, *75*, 8716 – 8719; h) X. Dou, F. Zhong, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 13945 – 13948; For other methods, see: i) F. Ozawa, A. Kubo, Y. Matsumoto, T. Hayashi, *Organometallics* **1993**, *12*, 4188 – 4196; j) D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *J. Am. Chem. Soc.* **2001**, *123*, 12095 – 12096.

[4] a) V. Cadierno, J. Gimeno, N. Nebra, *Adv. Synth. Catal.* **2007**, *349*, 382 – 394; b) R. Sanz, D. Miguel, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Org. Lett.* **2007**, *9*, 727 – 730; c) X. Feng, Z. Tan, D. Chen, Y. Shen, C.-C. Guo, J. Xiang, C. Zhu, *Tetrahedron Lett.* **2008**, *49*, 4110 – 4112; d) W. Ji, Y. Pan, S. Zhao, Z. Zhan, *Synlett* **2008**, 3046 – 3052; e) Y. Pan, S. Zhao, W. Jin, Z. Zhan, *J. Comb. Chem.* **2009**, *11*, 103 – 109; f) G. Aridoss, K. K. Laali, *Tetrahedron Lett.* **2011**, *52*, 6859 – 6864.

[5] a) Y.-F. Chen, H.-F. Wang, Y. Wang, Y.-C. Luo, H.-L. Zhu, P.-F. Xu, *Adv. Synth. Catal.* **2010**, *352*, 1163 – 1168; b) X. Meng, S. Kim, *Synlett* **2012**, 1960 – 1964.

[6] For reviews, see: a) N. Ljungdahl, N. Kann, *Angew. Chem.* **2009**, *121*, 652 – 654; *Angew. Chem. Int. Ed.* **2009**, *48*, 642 – 644; b) Y. Miyake, S. Uemura, Y. Nishibayashi, *ChemCatChem* **2009**, *1*, 342 – 356; c) R. J. Detz, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2009**, 6263 – 6276; d) C.-H. Ding, X.-L. Hou, *Chem. Rev.* **2011**, *111*, 1914 – 1937; e) Y. Nishibayashi, *Synthesis* **2012**, 489 – 503; f) E. B. Bauer, *Synthesis* **2012**, 1131 – 1151; For selected examples, see: g) R. J. Detz, M. M. E. Delville, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem.* **2008**, *120*, 3837 – 3840; *Angew. Chem. Int. Ed.* **2008**, *47*, 3777 – 3780; h) G. Hattori, H. Matsuzawa,

Y. Miyake, Y. Nishibayashi, *Angew. Chem.* **2008**, *120*, 3841 – 3843; *Angew. Chem. Int. Ed.* **2008**, *47*, 3781 – 3783; i) G. Hattori, A. Yoshida, Y. Miyake, Y. Nishibayashi, *J. Org. Chem.* **2009**, *74*, 7603 – 7607; j) P. Fang, X.-L. Hou, *Org. Lett.* **2009**, *11*, 4612 – 4615; k) G. Hattori, Y. Miyake, Y. Nishibayashi, *ChemCatChem* **2010**, *2*, 155 – 158; l) G. Hattori, K. Sakata, H. Matsuzawa, Y. Tanabe, Y. Miyake, Y. Nishibayashi, *J. Am. Chem. Soc.* **2010**, *132*, 10592 – 10608; m) R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra, J. H. van Maarseveen, *Chem. Eur. J.* **2011**, *17*, 5921 – 5930; n) A. Yoshida, G. Hattori, Y. Miyake, Y. Nishibayashi, *Org. Lett.* **2011**, *13*, 2460 – 2463; o) A. Yoshida, M. Ikeda, G. Hattori, Y. Miyake, Y. Nishibayashi, *Org. Lett.* **2011**, *13*, 592 – 595; p) C. Zhang, X.-H. Hu, Y.-H. Wang, Z. Zheng, J. Xu, X.-P. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 9585 – 9588; q) C. Zhang, Y.-H. Wang, X.-H. Hu, Z. Zheng, J. Xu, X.-P. Hu, *Adv. Synth. Catal.* **2012**, *354*, 2854 – 2858; r) T. Mino, H. Taguchi, M. Hashimoto, M. Sakamoto, *Tetrahedron: Asymmetry* **2013**, *24*, 1520 – 1523; s) F.-Z. Han, F.-L. Zhu, Y.-H. Wang, Y. Zou, X.-H. Hu, S. Chen, X.-P. Hu, *Org. Lett.* **2014**, *16*, 588 – 591; t) Y. Zhou, F.-L. Zhu, Z.-C. Duan, Y.-H. Wang, D.-Y. Zhang, Z. Cao, Z. Zheng, X.-P. Hu, *Tetrahedron Lett.* **2014**, *55*, 2033 – 2036; u) F.-L. Zhu, Y. Zou, D.-Y. Zhang, Y.-H. Wang, X.-H. Hu, S. Chen, J. Xu, X.-P. Hu, *Angew. Chem.* **2014**, *126*, 1434 – 1438; *Angew. Chem. Int. Ed.* **2014**, *53*, 1410 – 1414.

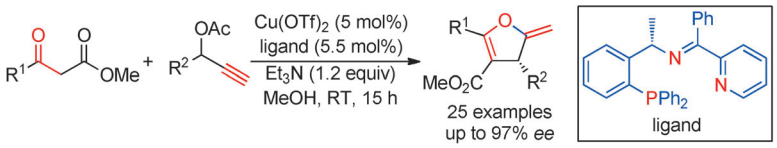
[7] CCDC 1004895 ((*R*)-**3ea**) and CCDC 1004897 ((*R*,*R*)-**6ea**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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

Communications

Asymmetric Catalysis

F.-L. Zhu, Y.-H. Wang, D.-Y. Zhang, J. Xu, X.-P. Hu* ——————— ■■■■–■■■■



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

The combination of $Cu(OTf)_2$ and a chiral tridentate P,N,N ligand as the catalyst enabled the title reaction, giving a variety of 2-methylene-2,3-dihydrofurans in good yields and with good to high enantioselectivities. Furthermore, the exocyclic methylene group can be hydrogenated in a highly diastereoselective fashion to give unusual *cis*-2,3-dihydrofuran derivatives.