Communication

Enantioselective Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds

Durga Prasad Hari, and Jerome Waser

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 16 Jun 2017

Enantioselective Copper-Catalyzed Oxy-Alkynylation of Diazo Compounds

Durga Prasad Hari and Jerome Waser

Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland.

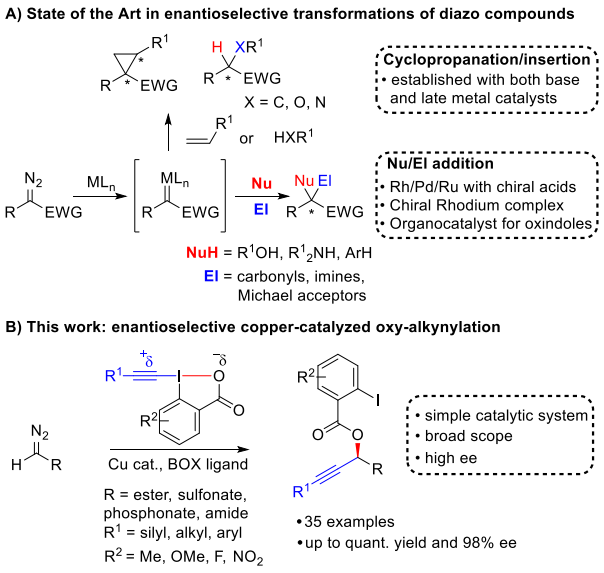
Supporting Information Placeholder

ABSTRACT: Enantioselective catalytic methods allowing the addition of both a nucleophile and an electrophile onto diazo compounds give a fast access into important building blocks. Herein, we report the highly enantioselective oxyalkynylation of diazo compounds using ethynylbenziodoxol-(on)e (EBX) reagents and a simple copper bisoxazoline (BOX) catalyst. The obtained α-benzoyloxy propargylic esters are useful building blocks, which are difficult to synthesize in enantiopure form using other methods. The obtained products could be efficiently transformed into vicinal diols and α-hydroxy propargylic esters without loss in enantiopurity.

Due to the different biological and optical properties of enantiomers, the synthesis of enantiopure compounds is an important field of research in organic chemistry. In this respect, enantioselective metal-catalyzed reactions of diazo compounds proceeding via carbenoid intermediates have been highly successful.[1] Asymmetric cyclopropanation and insertion into carbon or heteroatom- hydrogen bonds are now broadly used for the asymmetric synthesis of important building blocks. The generation of ylides by reaction of electrophilic carbenes with nucleophiles opened the way for [2,3] sigmatropic rearrangements and cycloaddition reactions.[2] Recently, researchers have focused on direct reactions of ylides generated from diazo compounds with electrophiles, allowing the introduction of more diverse functionalities on the carbon center.[3] The development of enantioselective variations of such processes is highly challenging. Recent breakthroughs have been realized based on elegant cooperative catalytic systems involving late metal catalysts such as rhodium/iridium,[4] palladium[5] and ruthenium,[6] and either a chiral phosphoric or Lewis acid (Scheme 1A). Nevertheless, this approach is limited to electrophilic partners that can be activated by Brønsted or Lewis acids, and it is based on a relative complex dual catalyst system. Transformations relying on a single chiral catalyst remain extremely rare in this new type of carbene transformations, including two examples of rhodium catalysts[7] and an organocatalytic system specific to diazo compounds derived from oxindoles.[8]

Surprisingly, despite their success in enantioselective cyclopropanation and X-H insertion reactions,[9] copper catalysts have been used so far only in racemic multi-component reactions involving diazo compounds.[10] Recently, our group developed a copper-catalyzed oxyalkynylation of diazo compounds[11] based on the use of EthynylBenziodoXolones (EBX) reagents.[12] Herein, we report the successful development of an enantioselective variation of this transformation, which constitutes the first asymmetric simultaneous introduction of an alkyne and an ester onto a diazo compound (Scheme 1B). Importantly, the reaction required a single copper catalyst bearing a broadly available BOX ligand, and gave products in high yield with up to 98% *ee*. The obtained propargylic benzoyloxy esters are useful building blocks, which are difficult to access using traditional methods, such as alkyne addition to aldehydes,[13] due to the sensitivity of the products and required starting materials to basic conditions.[14] Furthermore, they could be easily transformed into other important building blocks, such as propargylic alcohols.

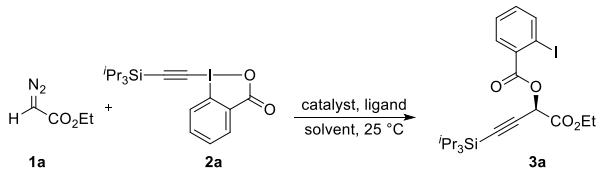
Scheme 1. Enantioselective transformations of diazo compounds.



We started our investigations by screening various ligands,[15] using ethyl diazoacetate (**1a**) with 1-[(tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)- one (TIPS-EBX, **2a**) and $Cu(OTf)_2$ as the copper source (Table 1).[16] Several classes of ligands, such as diimines, Salen, Phox or biphos-

phines gave either low selectivity or low conversion.[15] ^{t}Bu-BOX ligand **4a** gave the desired propargylic ester **3a** in excellent yield with a promising 56% ee (entry 1). The use of cyclopropyl and cyclopentyl derived BOX ligands (**4b** and **4c**) didn't improve the enantioselectivity (entries 2 and 3). Indane-BOX ligand **4d** gave results identical to the ones obtained with ligand **4a**, whereas a slightly better enantioselectivity was observed with cyclopropyl substituted ligand **4e** (entries 4 and 5). Among the solvents tested[15] (entries 6-8), chlorobenzene emerged as the best solvent (84% yield with 70% *ee*, entry 7). Generating a cationic complex in situ from $AgSbF_6$ and CuCl provided a slight improvement (entry 9). No reaction was observed when using $AgClO_4$ or NaBARF(entries 10 and 11). $AgNTf_2$ gave the desired product in 91% yield and 84% ee (entry 12). Without $AgNTf_2$, no product was obtained (entry 13). Finally, the enantioselectivity could be improved to 90% by lowering the concentration of the reaction (entry 14).

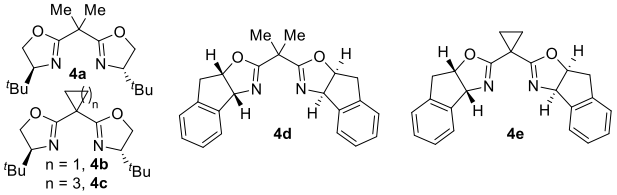
Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

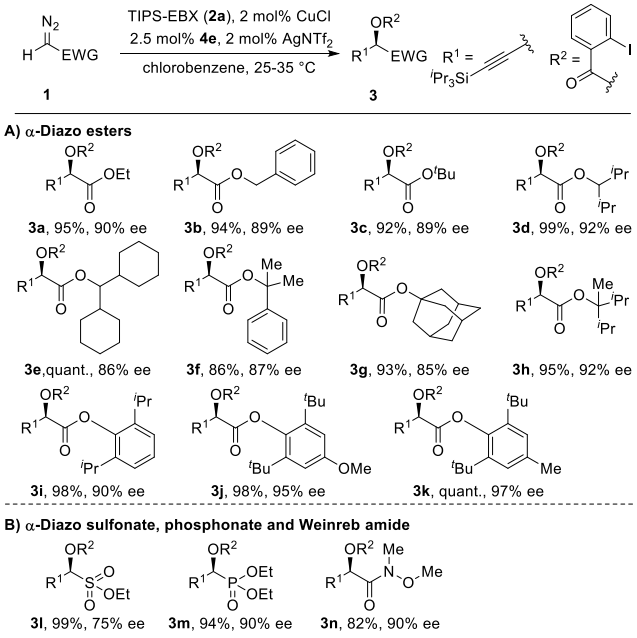
Entry	Catalyst	Ligand	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Cu(OTf)_2$	**4a**	DCE	0.5	97	56[e]
2	$Cu(OTf)_2$	**4b**	DCE	0.5	98	55[e]
3	$Cu(OTf)_2$	**4c**	DCE	0.5	98	54[e]
4	$Cu(OTf)_2$	**4d**	DCE	2	98	54
5	$Cu(OTf)_2$	**4e**	DCE	0.5	97	62
6	$Cu(OTf)_2$	**4e**	DCM	0.5	98	40
7	$Cu(OTf)_2$	**4e**	PhCl	2	84	70
8	$Cu(OTf)_2$	**4e**	xylene	2	79	69
9	$CuCl/AgSbF_6$	**4e**	PhCl	1	89	72
10	$CuCl/AgClO_4$	**4e**	PhCl	24	<5	nd[f]
11	CuCl/NaBARF	**4e**	PhCl	24	<5	nd
12	$CuCl/AgNTf_2$	**4e**	PhCl	18	91	84
13	CuCl	**4e**	PhCl	24	<5	nd
14[d]	$CuCl/AgNTf_2$	**4e**	PhCl	18	95	90

[a]Reaction conditions: 0.30 mmol ethyldiazoacetate (**1a**), 0.15 mmol TIPS-EBX (**2a**), copper catalyst (2.0 mol%), ligand (2.5 mol%), solvent (0.05 M), for entries 9-12 and 14: AgX or NaBARF (2.0 mol%). [b]Yield after purification by column chromatography. [c]Obtained by chiral HPLC. [d]0.025 M instead of 0.05 M. [e] The opposite enantiomer of the product was obtained. [f]nd = not determined.



To further improve the enantioselectivity, we investigated the influence of the structure of the α-diazo ester (Scheme 2A). Aliphatic diazoesters of different steric bulk afforded products **3a-h** in 85-92% *ee*. Hindered aryl diazo esters[18] provided higher enantioselectivities (up to 97%) (products **3i-k**). The reaction was not limited to α-diazo esters. Both ethyl diazomethanesulfonate and diethyl (diazomethyl)phosphonate gave the desired product **3l** and **3m** in high yield and moderate to high selectivity (Scheme 2B). Finally, diazo Weinreb amide also delivered the product **3n**, which open up possibilities for further derivatization.[19]

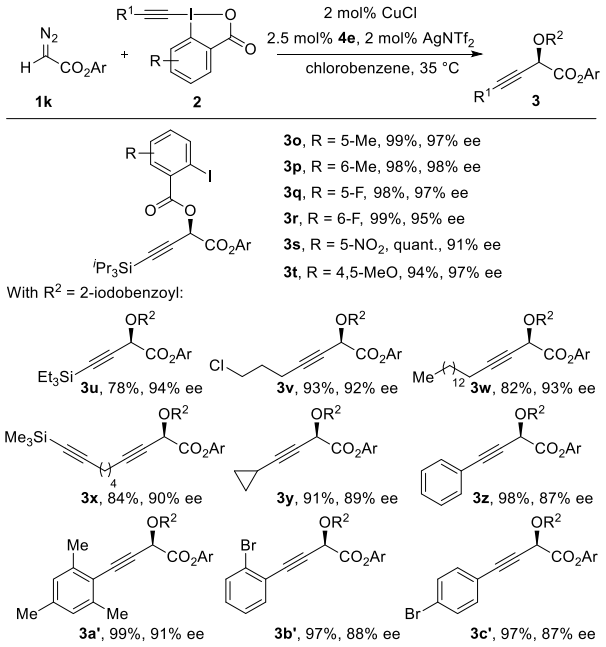
Scheme 2. Scope of diazo compounds with TIPS-EBX (2a).



We next examined the scope of R-EBX reagents using 2,6-di-*tert*-butyl-4-methylphenyl 2- diazoacetate (**1k**) (Scheme 3). Electron-donating and -withdrawing groups were well tolerated on the aryl ring of TIPS-EBX (**2a**) (products **30-t**). The reaction was successful with a triethyl silyl group (product **3u**), whereas no product could be isolated with a trimethylsilyl group. Aliphatic EBX reagents bearing substituents such as long alkyl chain, chloro, TMS-alkyne and a cyclopropyl group worked efficiently in this transformation, giving products **3v-y**. Finally, EBX reagents bearing aryl substituents on the alkyne led to the desired products **3z-c'** in excellent yields and good enantioselectivities.

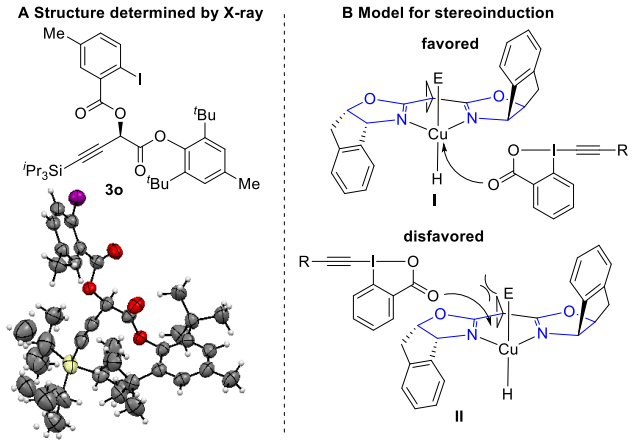
The absolute configuration of **30** could be determined by X-ray analysis (Figure 1A).[20] The observed stereochemistry would be in agreement with an attack of the carboxylate of the reagent in the free quadrant opposite to the ester group on a three coordinate copper carbene complex with a 90° angle between the ligand and the carbene plan,[9g] followed by stereospecific alkynylation with retention of configuration (**I**, Figure 1B). Further studies will be needed to support the proposed stereoinduction model.

Scheme 3. Scope of R-EBX reagents. Ar = 2,6-di-*tert*-butyl-4-methylphenyl.



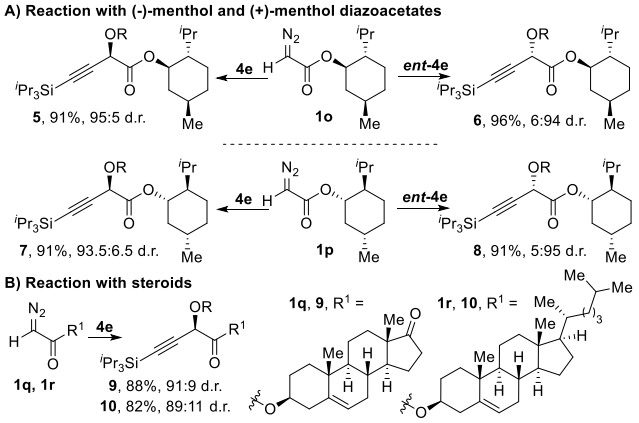
When (-) menthol diazoacetate **1o** was subjected to the standard conditions, the desired product **5** was obtained in good yield with 95:5 d.r. (Scheme 4A).[21] The use of the *S*-enantiomer ***ent*-4i** of ligand **4i** afforded the other diastereomer **6** in good yield with 6:94 d.r, demonstrating that the configuration at the new stereocenter could be controlled by the chiral catalyst. Similar results were obtained with (+) menthol diazoacetate **1p**. All four diastereomers can therefore be obtained in good yield and selectivity. Good ligand control over the stereoselectivity could also be achieved with more complex diazo compounds **1q** and **1r** derived from steroids (Scheme 4B).

Figure 1. Absolute configuration and stereoinduction model.



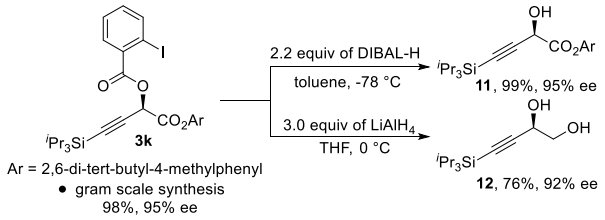
The obtained products were then further transformed into useful building blocks for organic synthesis (Scheme 5). Compound **3k** was synthesized on gram scale in 98% yield with 95% *ee*. The benzoyl group could be readily removed using DIBAL-H, thus affording the α-hydroxy propargylic ester **11** in 99% yield with retention of enantiopurity. Furthermore, vicinal diol **12**[22] could be synthesized by reduction of **3k** using $LiAlH_4$. Such alkynyl diol building blocks are useful in synthetic chemistry, but are usually accessed via longer multi step procedures.[23]

Scheme 4. Reactions with menthol and steroids esters.



Reaction conditions: 0.30 mmol diazoacetate (**1**), 0.15 mmol TIPS-EBX (**2a**), CuCl (2.0 mol%), ligand (2.5 mol%), $AgNTf_2$ (2 mol%), PhCl (0.025 M), 25 °C. R = 2-iodobenzoyl.

Scheme 5. Scale up and product modifications.



In summary, we have developed a highly enantioselective oxyalkynylation of diazo compounds. This transformation is the first example of copper-catalyzed addition of both a nucleophile and an electrophile onto a carbenoid intermediate. A broad range of EBX reagents and diazo compounds were well tolerated. The reaction proceeds under mild conditions, giving highly functionalized products with excellent yields and selectivities. The obtained products were efficiently transformed into useful building blocks, such as α-hydroxy propargylic esters and vicinal diols, in a single step without loss of enantioselectivity. Further extending this methodology to other diazo compounds and hypervalent iodine reagents is currently under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

jerome.waser@epfl.ch

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the European Research Council (ERC; Starting Grant iTools4MC, number 334840) and the EPFL for financial support. We thank Dr. Scopelliti Rosario and Dr. Fadaei Tirani Farzaneh from ISIC-EPFL for the X-ray studies.

REFERENCES

(1) (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.

(2) Selected examples: (a) Y. Nishibayashi, K. Ohe, S. Uemura, *J. Chem. Soc., Chem. Commun.* **1995**, 1245. (b) M. P. Doyle, D. C. Forbes, M. M. Vasbinder, C. S. Peterson, *J. Am. Chem. Soc.* **1998**, *120*, 7653. (c) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. I. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417. (d) M. Ma, L. Peng, C. Li, X. Zhang, J. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 15016.

(3) Reviews: (a) Guo, X.; Hu, W. *Acc. Chem. Res.* **2013**, *46*, 2427. (b) Zhang, D.; Hu, W. *Chem. Rec.* **2017**, *17*, 1.

(4) (a) Huang, H.; Guo, X.; Hu, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 1337. (b) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (c) Xu, X. F.; Zhou, J.; Yang, L. P.; Hu, W. H. *Chem. Commun.* **2008**, 6564. (d) Guan, X. Y.; Yang, L. P.; Hu, W. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2190. (e) Jiang, J.; Xu, H. D.; Xi, J. B.; Ren, B. Y.; Lv, F. P.; Guo, X.; Jiang, L. Q.; Zhang, Z. Y.; Hu, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (f) Qiu, H.; Li, M.; Jiang, L. Q.; Lv, F. P.; Zan, L.; Zhai, C. W.; Doyle, M. P.; Hu, W. H. *Nature Chem.* **2012**, *4*, 733. (g) Jia, S.; Xing, D.; Zhang, D.; Hu, W. *Angew. Chem., Int. Ed.* **2014**, 53, 13098. (h) Zhang, D.; Zhou, J.; Xia, F.; Kang, Z.; Hu, W. *Nature Commun.* **2015**, *6*, 5801. (i) Alamsetti, S. K.; Spanka, M.; Schneider, C. *Angew. Chem., Int. Ed.* **2016**, 55, 2392. (j) Li, M. F.; Guo, X.; Jin, W. F.; Zheng, Q.; Liu, S. Y.; Hu, W. H. *Chem. Commun.* **2016**, 52, 2736.

(5) Zhang, D.; Qiu, H.; Jiang, L. Q.; Lv, F. P.; Ma, C. Q.; Hu, W. H. *Angew. Chem., Int. Ed.* **2013**, 52, 13356.

(6) Chen, D. F.; Zhao, F.; Hu, Y.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2014**, 53, 10763.

(7) (a) Zhou, C.-Y.; Wang, J.-C.; Wei, J.; Xu, Z.-J.; Guo, Z.; Low, K.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11376. (b) Ma, X. C.; Jiang, J.; Lv, S. Y.; Yao, W. F.; Yang, Y.; Liu, S. Y.; Xia, F.; Hu, W. H. *Angew. Chem., Int. Ed.* **2014**, 53, 13136.

(8) Wu, M. Y.; He, W. W.; Liu, X. Y.; Tan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 9409.

(9) Review: (a) Zhao, X.; Zhang, Y.; Wang, J. B. *Chem. Commun.* **2012**, *48*, 10162. Selected examples: (b) T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 4594. (c) E. C. Lee, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 12066. (d) J. M. Fraile, J. I. García, J. A. Mayoral, M. Roldán, *Org. Lett.* **2007**, *9*, 731. (e) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834. (f) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 12616. (g) S.-F. Zhu, C. Chen, Y. Cai, Q.-L. Zhou, *Angew. Chem., Int. Ed.* **2008**, *47*, 932. (h) C. J. Flynn, C. J. Elcoate, S. E. Lawrence, A. R. Maguire, *J. Am. Chem. Soc.* **2010**, *132*, 1184. (i) G. Jiménez-Osés, E. Vispe, M. Roldán, S. Rodríguez-Rodríguez, P. López-Ram-de-Viu, L. Salvatella, J. A. Mayoral, J. M. Fraile, *J. Org. Chem* **2013**, *78*, 5851.

(10) (a) Zhu, Y. G.; Zhai, C. W.; Yang, L. P.; Hu, W. H. *Chem. Commun.* **2010**, *46*, 2865. (b) Du, Z.; Xing, Y. P.; Lu, P.; Wang, Y. G. *Org. Lett.* **2015**, *17*, 1192. (c) Day, J.; McKeever-Abbas, B.; Dowden, J. *Angew. Chem., Int. Ed.* **2016**, 55, 5809. (d) Goudedranche, S.; Besnard, C.; Egger, L.; Lacour, J. *Angew. Chem., Int. Ed.* **2016**, 55, 13775. (e) Muthusamy, S.; Kumar, S. G. *Org. Biomol. Chem.* **2016**, *14*, 2228. (f) Zhang, T. S.; Hao, W. J.; Wang, N. N.; Li, G. G.; Jiang, D. F.; Tu, S. J.; Jiang, B. *Org. Lett.* **2016**, *18*, 3078.

(11) Hari, D. P.; Waser, J. *J. Am. Chem. Soc.* **2016**, *138*, 2190.

(12) Discovery: (a) Ochiai, M.; Masaki, Y.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 5511. (b) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547. Reviews: (c) Kaschel, J.; Werz, D. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 8876. (d) Waser, J. *Top. Curr. Chem.* 2016, **373**, 187. (e) Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. *Angew. Chem., Int. Ed.* **2016**, 55, 4436. For another example of multi-bond formation on diazo compounds with hypervalent iodine reagents, see: (f) Yuan, W. M.; Eriksson, L.; Szabo, K. J. *Angew. Chem., Int. Ed.* **2016**, 55, 8410.

(13) (a) Frantz, D. E.; Fässler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757. (c) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(14) Only few asymmetric approaches have been reported to access such building blocks: Enzymatic resolution: (a) Ogawa, J.; Xie, S.-X.; Shimizu, S. *Appl. Microbiol. Biotechnol.* **1999**, *51*, 53. (b) Weng, S.-S.; Shen, M.-W.; Kao, J.-Q.; Munot, Y. S.; Chen, C.-T. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 3522. (c) Saravanan, T.; Chadha, A. *Tetrahedron: Asymmetry* **2010**, *21*, 2973. (d) Pérez-Estrada, S.; Joseph-Nathan, P.; Jiménez-Vázquez, H. A.; Medina-López, M. E.; Ayala-Mata, F.; Zepeda, L. G. *J. Org. Chem.* **2012**, *77*, 1640. (e) Chen, H.-B.; Lai, W.-H.; Zhao, Y.; Qin, D.-D.; Ruan, Y.-P.; Zhou, Z.-H. *Synlett* **2014**, *25*, 809. For enantioselective reduction of ynones, see: (f) Prévost, S.; Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2011**, *353*, 3213. For another enantioselective approach, see: (g) Wang, L.; Liu, R.; Lv, C.; Ou, J.; Liu, F.; Liu, S.; Wang, M.; Zhong, J. *Tetrahedron: Asymmetry* **2013**, *24*, 173.

(15) See Supporting Information for a full list of reaction conditions and ligands.

(16) $Cu(CH_3CN)_4\ BF_4$ was used for the racemic reaction. See ref. 11.

(17) Ye, M.-C.; Li, B.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6108.

(18) (a) M. P. Doyle, V. Bagheri, T. J. Wandless, N. K. Harn, D. A. Brinker, C. T. Eagle, K. L. Loh, *J. Am. Chem. Soc.* **1990**, *112*, 1906. (b) Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046.

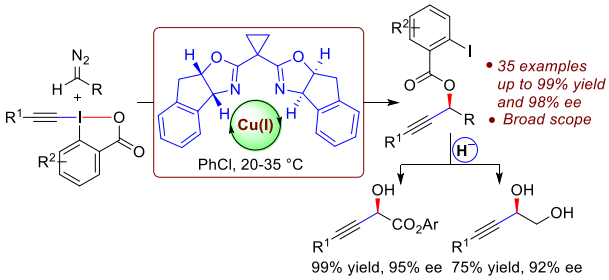
(19) No reaction with alkyl-, aryl- and vinyl-substituted diazo compounds was observed, due to the lower reactivity of the copper bisoxazoline complexes compared to $Cu(CH_3CN)_4\ BF_4$.

(20) CCDC 1534166, see the Supporting Information, the configuration of the other substrates was assigned by analogy.

(21) The use of achiral ligand resulted in low selectivity (d.r. = 54:46).

(22) The enantioselectivity of **12** was determined after derivatization (see the Supporting Information).

(23) (a) Yadav, J. S.; Chander, M. C.; Srinivas Rao, C. *Tetrahedron Lett.* **1989**, *30*, 5455. (b) Gung, B. W.; Kumi, G. *J. Org. Chem.* **2003**, *68*, 5956. (c) Meijler, M. M.; Hom, L. G.; Kaufmann, G. F.; McKenzie, K. M.; Sun, C.; Moss, J. A.; Matsushita, M.; Janda, K. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2106.


N2
H
R
R1
O
O
R2
H
O
N
N
O
H
H
H
Cu(I)
PhCl, 20-35 °C
R2
I
O
O
R
R1
H
• 35 examples
up to 99% yield
and 98% ee
• Broad scope
OH
CO2Ar
R1
99% yield, 95% ee
OH
OH
R1
75% yield, 92% ee