



Unexpected chiral vicinal tetrasubstituted diamines via borylcopper-mediated homocoupling of isatin imines

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Letter

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Abstract

Addressing the asymmetric synthesis of oxindole-based α -aminoboronic acids, instead of the expected products we disclosed the efficient homocoupling of oxindole-based *N*-*tert*-butanesulfinyl imines, with the generation of chiral, quaternary 1,2-diamines in a mild and completely stereoselective way. The obtained 3,3'-bisoxindole derivatives were fully characterized by NMR and single-crystal X-ray diffraction analysis and proved to be single diastereoisomers and atropisomers. A plausible mechanism for the one-pot Cu(II)-catalyzed Bpin addition to the isatin-derived ketimine substrate and subsequent homocoupling is described.

Introduction

As bioisosteres of carboxylic acid derivatives, boronic acids have recently emerged as a novel chemotype in drug design, with a number of boron-containing compounds recently being approved by the FDA [1-4]. In particular, α - and β -aminoboronic acids are commonly utilized as key intermediates for the synthesis of boron-containing peptidomimetics, which have been demonstrated to be efficient covalent ligands and valuable protease inhibitors endowed with various biological activities [5,6].

Going on with our interest in the synthesis of 3,3-disubstituted oxindoles [7-11] and also of aminoboronic acids [12], we

recently exploited a molecular hybridization strategy to synthesize chiral oxindole-based β -aminoboronic acids and spiro derivatives [13]. Apart from our work and a quite recent report describing a useful Cu-catalyzed enantioselective intramolecular transformation [14], the insertion of a boron atom into chiral oxindoles is scarcely reported.

Continuing with such previous project, next we looked at the copper-mediated reaction of isatin-derived, optically pure sulfinyl ketimines with bis(pinacolato)diboron, as a potential way to access oxindole-based α -aminoboronates. The asymmetric synthesis of diverse α -aminoboronic acids by diastereo-

selective Cu(I)-catalyzed borylation of *N-tert*-butanesulfinyl aldimines was described by Ellman and co-workers for the first time in 2008 [15] and next further developed with a more stable Cu(II) catalyst in 2014 [16].

Herein, we describe the unexpected results achieved by our work, that is the obtainment of unprecedented, bisoxindole-based, vicinal, tetrasubstituted diamines. Bisoxindoles represent a particularly intriguing class of compounds, because of their interesting biological activities and because they can serve as key synthetic intermediates in the construction of complex natural products [17–23]. Particularly challenging is the placement of the two C3/C3' contiguous quaternary stereogenic centers, just as they are found in various alkaloids, such as those belonging to the bis(cyclotryptamine) family [24–27].

In light of these considerations and as, to our knowledge, no borylcopper-mediated homocoupling of *N-tert*-butanesulfinyl imines have been documented before, we consider useful to share our findings and to accurately describe the obtained products.

Results and Discussion

We began our investigation using the known (*R*)-1-methylisatin-derived *N-tert*-butanesulfinyl ketimine **1a**, bis(pinacolato)diboron, CuSO₄/(Cy)₃P catalyst and benzylamine, as reported in Scheme 1. The first reaction was carried out at room temperature in toluene/water (5:1), as described by Ellman and co-workers, but the expected α -aminoboronate could not be isolated. Extensive hydrolysis of the starting ketimine occurred, allowing only the recovery of the 1-methylisatin precursor.

In the light of this initial outcome, we started a detailed screening of reaction conditions (Table 1), evaluating firstly different amines (Table 1, entries 1–5), in place of benzylamine. Using DIPEA, the new product **2a** was obtained in 31% yield, even if together with 1-methylisatin and other impurities. Aiming to improve the fruitful conversion of substrate **1a**, we considered to reduce the amount of water to the minimum

necessary to solubilize the copper sulfate. Thus, performing the reaction in toluene/water 100:1, ketimine hydrolysis was almost entirely prevented and the yield of compound **2a** raised to 52% (Table 1, entry 6). With regard to the ligand (Table 1, entries 7 and 8), PPh₃ behaved most effectively, further promoting the conversion of the substrate. Other changes in reaction conditions, such as heating at 70 °C, increasing the amount of copper catalyst to 10 mol % and switching the copper salt from CuSO₄ to the more soluble Cu(OTf)₂, did not improve the yield significantly (Table 1, entries 9–11), while the yield raised up to 68% when 0.5 equivalents of base were used (Table 1, entry 12). Finally, in order to shed light on the reaction mechanism (see below), three control experiments were carried out. Under anhydrous conditions (Table 1, entry 13), conversion of the starting ketimine did not take place. Also conducting the reaction in the absence of B₂pin₂ (Table 1, entry 14) or copper salt (Table 1, entry 15), respectively, no reaction could be observed and the substrate was recovered together with small amounts of the 1-methylisatin precursor.

From the reaction run under the optimized conditions (Table 1, entry 12) followed by flash chromatography, the unprecedented bisoxindole **2a** was fully characterized by high-resolution mass spectrometry and by one- and two-dimensional NMR analysis. In particular, from HSQC, HMBC and COSY experiments all single frequencies could be safely assigned in the ¹H and ¹³C NMR spectra, allowing the complete spin system reconstruction for both the oxindole-based units. Furthermore, from NOESY experiment, the unique *anti* disposition of the two *t*-Bu–SO–NH substituents along the C3–C3' bond could be assessed, thus demonstrating the complete diastereoselectivity of the reaction (see Supporting Information File 1).

All stereochemical implications were fully confirmed by single-crystal X-ray diffraction analysis, which was performed on well-formed prismatic crystals of compound **2a** (Figure 1) [28].

Compound **2a** is chiral and crystallizes in the orthorhombic space group *P*2₁2₁2₁. The presence of sulfur anomalous scatterers allowed to unequivocally establish the absolute configura-

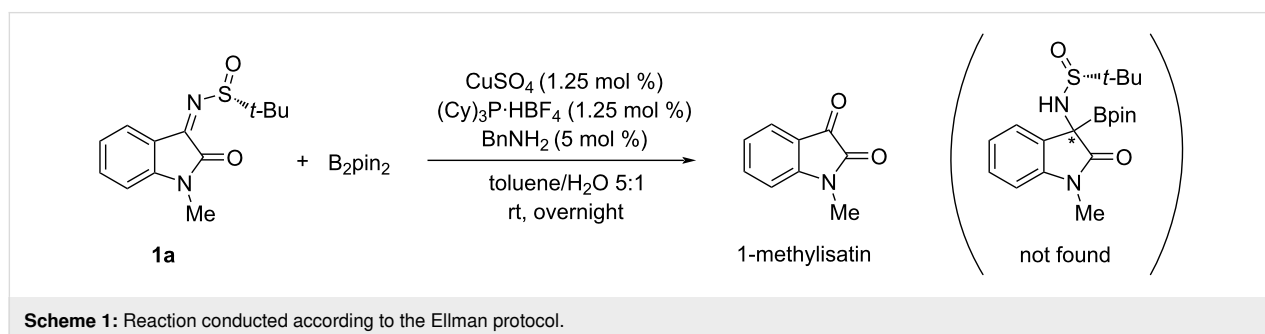
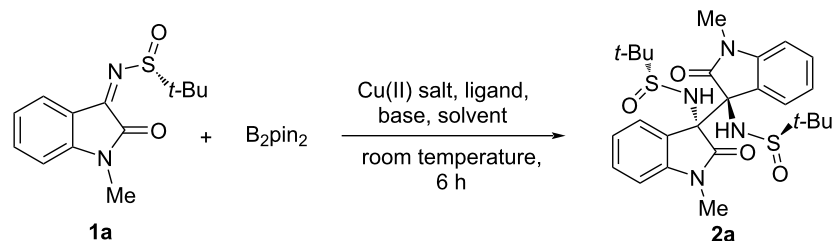


Table 1: Screening of the reaction conditions for compound **2a**.^a

entry	Cu(II) salt	ligand	base	solvent	yield 2a [%] ^b
1	CuSO ₄	(Cy) ₃ P·HBF ₄	Py	toluene/H ₂ O 5:1	6
2	CuSO ₄	(Cy) ₃ P·HBF ₄	DMAP	toluene/H ₂ O 5:1	n. d.
3	CuSO ₄	(Cy) ₃ P·HBF ₄	DABCO	toluene/H ₂ O 5:1	n. d.
4	CuSO ₄	(Cy) ₃ P·HBF ₄	TEA	toluene/H ₂ O 5:1	23
5	CuSO ₄	(Cy) ₃ P·HBF ₄	DIPEA	toluene/H ₂ O 5:1	31
6	CuSO ₄	(Cy) ₃ P·HBF ₄	DIPEA	toluene/H ₂ O 100:1	52
7	CuSO ₄	(<i>o</i> -tol) ₃ P	DIPEA	toluene/H ₂ O 100:1	62
8	CuSO ₄	(Ph) ₃ P	DIPEA	toluene/H ₂ O 100:1	66
9 ^c	CuSO ₄	(Ph) ₃ P	DIPEA	toluene/H ₂ O 100:1	33
10 ^d	CuSO ₄	(Ph) ₃ P	DIPEA	toluene/H ₂ O 100:1	61
11	Cu(OTf) ₂	(Ph) ₃ P	DIPEA	toluene/H ₂ O 100:1	66
12 ^e	CuSO ₄	(Ph) ₃ P	DIPEA	toluene/H ₂ O 100:1	68
13	CuSO ₄	(Ph) ₃ P	DIPEA	toluene/DMSO 100:1	n. r.
14 ^f	CuSO ₄	(Ph) ₃ P	DIPEA	toluene/H ₂ O 100:1	n. r.
15 ^g	–	–	DIPEA	toluene/H ₂ O 100:1	n. r.

^aReagents and conditions: ketimine **1a** (0.2 mmol), B₂pin₂ (1.5 equiv), Cu(II) salt (2.5 mol %), ligand (2.5 mol %), base (5 mol %), in solvent (0.7 M).

^bIsolated yields. ^cReaction heated at 70 °C. ^dReaction performed with 10% of CuSO₄ and PPh₃. ^eReaction performed with 0.5 equiv of DIPEA.

^fReaction performed in the absence of B₂pin₂. ^gReaction performed in the absence of Cu(II) salt and ligand. n. d. = not determined. n. r. = no reaction.

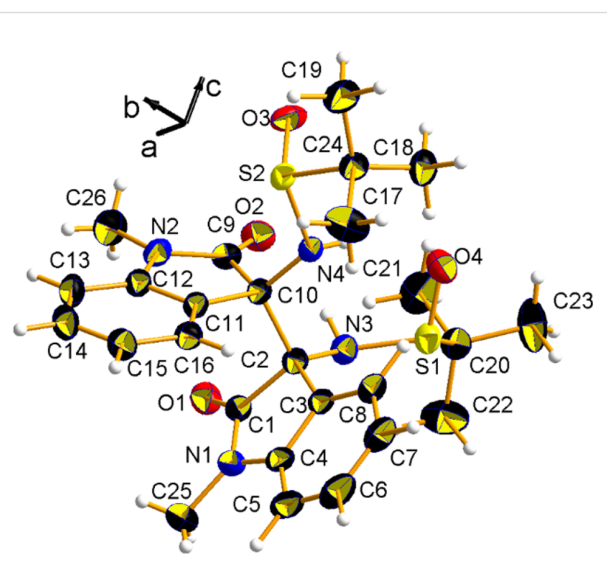


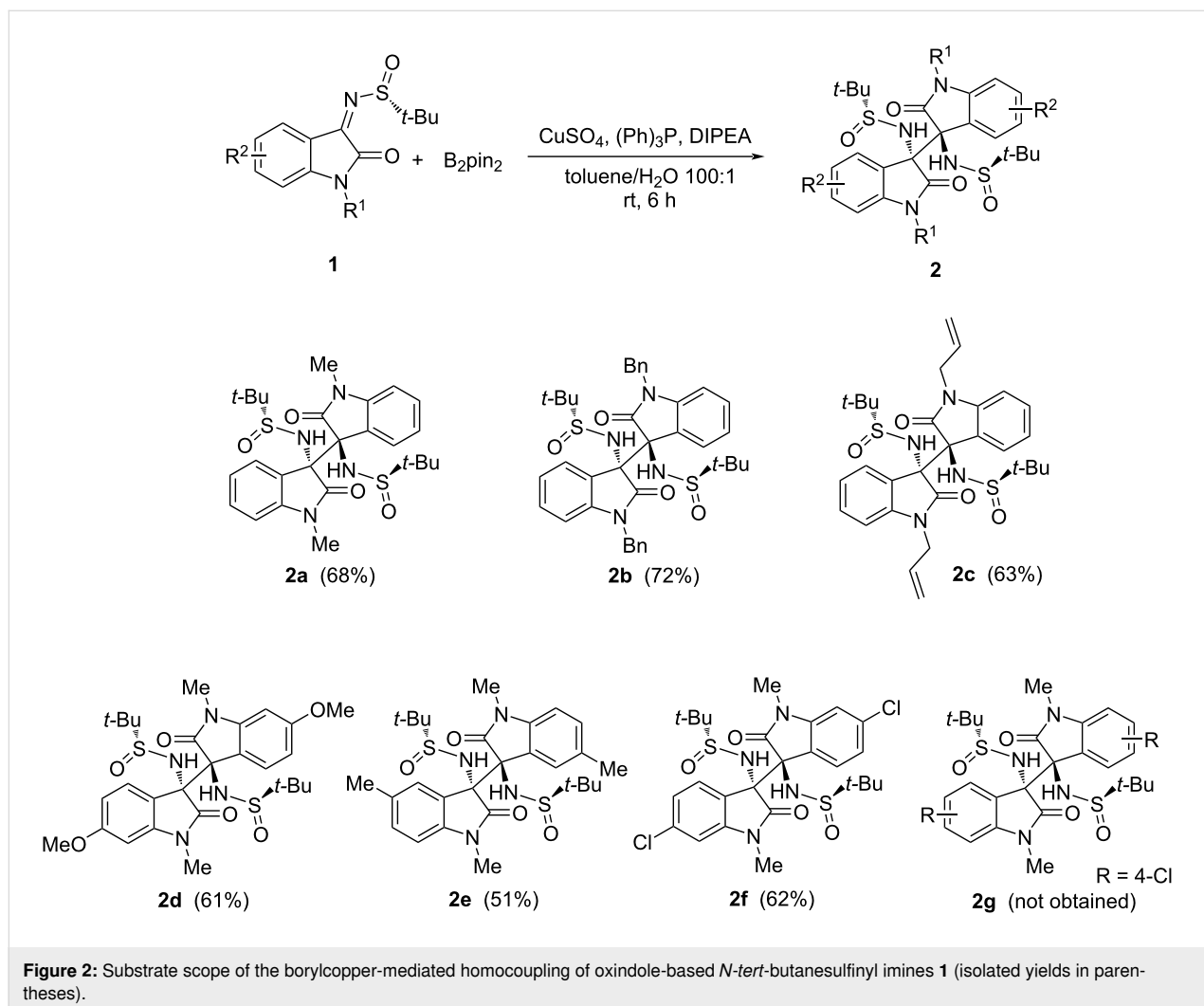
Figure 1: Asymmetric unit of **2a**, with the atom-numbering scheme. The crystallographic reference system is also shown. Thermal ellipsoids at rt were drawn at the 50% probability level. Atoms are represented with the usual colour code (C: black; N: blue; O: red; S: yellow; H: white).

tions, which reads *S* at the chiral center C2 and *R* at the C10 (C numbering as in Figure 1). The absolute configuration of the two sulfur stereogenic centers is confirmed to be *R*. Interestingly, the molecule does not bear any pseudo-mirror plane, that is, the observed conformer is asymmetric (C1) in itself, regardless the configuration of the two sulfonamide substituents. This peculiarity is likely due to the hindered rotation across the newly formed C–C bond, joining the two oxindole units. Such the C2–C10 single bond is quite long (1.58 Å), as expected due to crowding of the two facing oxindole systems. In the crystal, NH groups set up intramolecular hydrogen bonds with the O acceptors of the sulfonamide moieties (see Table 2), likely contributing to further stabilize the observed conformer.

Aiming to generalize the discovered transformation, a brief scope of the reaction with respect to the *N*-*tert*-butanesulfinyl imine substrate was next performed (Figure 2). The protecting group R¹ on the oxindole nitrogen atom was found to have a moderate effect on the reactivity, with R¹ = Bn giving the best yield (**2a–c**). *N*-Methylisatin ketimines with various R² residues were also evaluated. In the presence of substituents at the C5 or

Table 2: Intramolecular hydrogen bonds in **2a** at room temperature, which involve the NH groups with one keto oxygen (O2) and one sulfonamide oxygen (O4). Atom numbering as in Figure 1. The asymmetry of such interactions reflects the intrinsic asymmetry of the solid-state conformer.

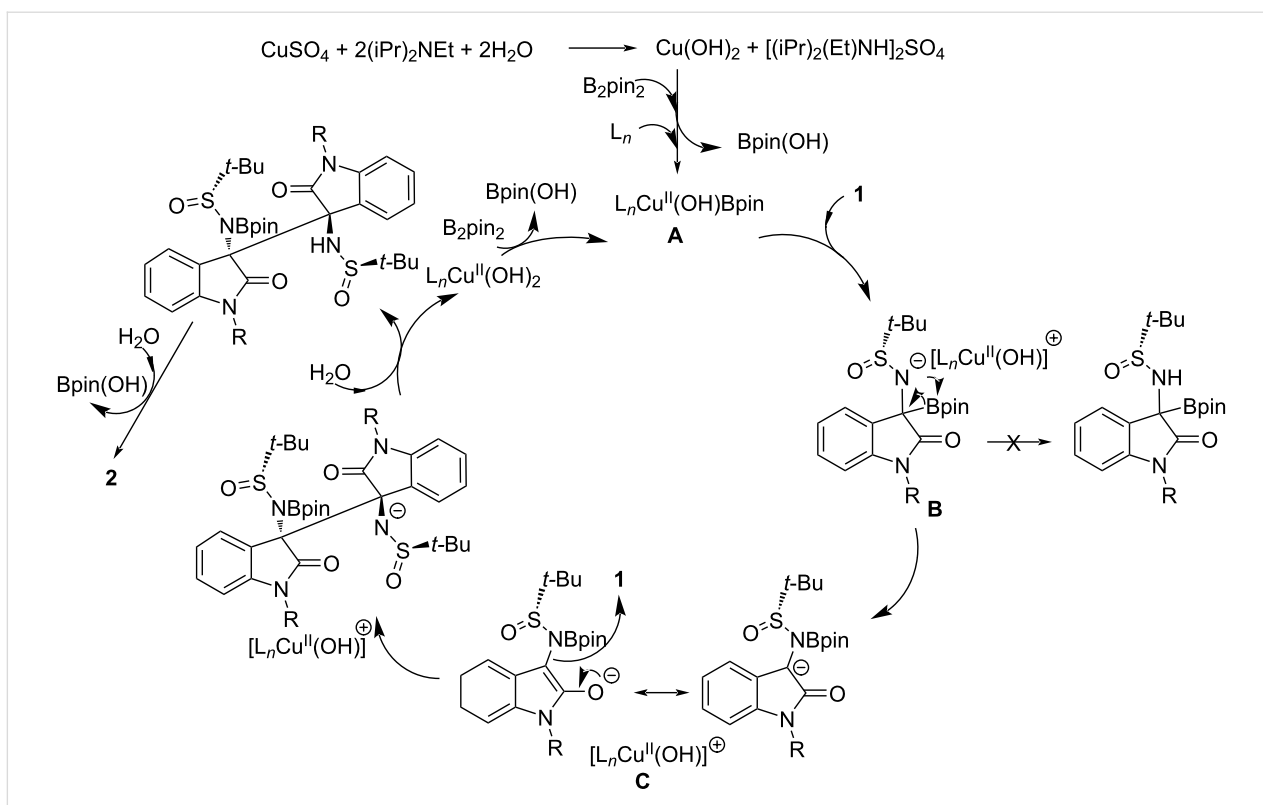
D–H...A	d_{D-H} [Å]	$d_{H...A}$ [Å]	d_{D-A} [Å]	α [deg]	symmetry
N3–H3N...O2	0.99(4)	2.03(4)	2.854(4)	139(3)	x, y, z
N4–H4N...O4	0.82(4)	2.21(4)	2.981(4)	157(4)	x, y, z



C6 position on the oxindole aromatic ring, such as electron-donating groups (6-OMe, **2d** and 5-Me, **2e**) and halogen substituents (6-Cl, **2f**), good yields of the corresponding quaternary 1,2-diamines were obtained. Instead, the presence of a substituent at the C4 position (4-Cl, **2g**) hinders the course of the reaction, likely due to its spatial proximity with the reaction center, and no homocoupling could be observed.

In order to rationalize the formation of bisoxindole products, besides relying on performed control experiments, we also refer

to the underdeveloped umpolung reactions of imines, considering, in particular, the copper-catalyzed process reported quite recently by Zhang, Hou and co-workers [29]. In our case, we presume the possible reaction mechanism shown in Scheme 2, which likely starts from the catalytic generation, in our experimental conditions, of the borylcopper(II) species **A**. Such copper complex proved to be not isolable, but could be easily generated in situ and may act as a genuine Cu(II) catalyst, with a labile coordination site [30]. According to Ellman's chemistry, the addition of Bpin to the C=N double bond of the



Scheme 2: Proposed mechanism for the borylcopper-mediated homocoupling of ketimines 1.

ketimine substrate **1** should actually take place, affording the intermediate **B**, the immediate precursor of our original target compound, namely the α -aminoboronate derivative. However, probably due to its high steric crowding, such intermediate spontaneously turns into the carbanion **C**, thus realizing the imine umpolung and allowing the cross-coupling reaction with the remaining electrophilic ketimine **1**. The complete diastereoselectivity would arise from the mutual approach of the two oxindole nuclei from the less hindered side, that is the one away from the bulky auxiliary *t*-Bu group. The presence of two NH-SO*t*-Bu substituents, preventing the free rotation around the C3–C3' bond, ensures the optical activity of the molecule, in accordance with the presence of a single atropisomer (absence of any pseudo-mirror plane), as also determined by single-crystal X-ray diffraction analysis.

Conclusion

In summary, we have disclosed a reaction protocol that allows efficient homocoupling of oxindole-based *N*-*tert*-butanesulfinyl imines and generation of chiral, quaternary 1,2-diamines in a mild and completely stereoselective way. The one-pot, simple experimental procedure makes this process a convenient and straightforward approach for the synthesis of enantiomerically pure vicinal diamines and structurally challenging bisoxindole natural products.

Supporting Information

Supporting Information File 1

Experimental part, NMR spectra and chirallographic data of compound **2a**.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-34-S1.pdf>]

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References

- Chatterjee, S.; Tripathi, N. M.; Bandyopadhyay, A. *Chem. Commun.* **2021**, *57*, 13629–13640. doi:10.1039/d1cc05481c
- Plescia, J.; Moitessier, N. *Eur. J. Med. Chem.* **2020**, *195*, 112270. doi:10.1016/j.ejmech.2020.112270
- Silva, M. P.; Saraiva, L.; Pinto, M.; Sousa, M. E. *Molecules* **2020**, *25*, 4323. doi:10.3390/molecules25184323

4. Diaz, D. B.; Yudin, A. K. *Nat. Chem.* **2017**, *9*, 731–742. doi:10.1038/nchem.2814
5. Andrés, P.; Ballano, G.; Calaza, M. I.; Catiaviela, C. *Chem. Soc. Rev.* **2016**, *45*, 2291–2307. doi:10.1039/c5cs00886g
6. Šterman, A.; Sosič, I.; Gobec, S.; Časar, Z. *Org. Chem. Front.* **2019**, *6*, 2991–2998. doi:10.1039/c9qo00626e
7. Gazzotti, S.; Manenti, M.; Lo Presti, L.; Silvani, A. *RSC Adv.* **2019**, *9*, 37788–37800. doi:10.1039/c9ra07712j
8. Rainoldi, G.; Beghini, F.; de Munnik, M.; Lo Presti, L.; Vande Velde, C. M. L.; Orru, R.; Lesma, G.; Ruijter, E.; Silvani, A. *ACS Comb. Sci.* **2018**, *20*, 98–105. doi:10.1021/acscombsci.7b00179
9. Rainoldi, G.; Faltracco, M.; Spatti, C.; Silvani, A.; Lesma, G. *Molecules* **2017**, *22*, 2016. doi:10.3390/molecules22112016
10. Rainoldi, G.; Faltracco, M.; Lo Presti, L.; Silvani, A.; Lesma, G. *Chem. Commun.* **2016**, *52*, 11575–11578. doi:10.1039/c6cc05838h
11. Rainoldi, G.; Sacchetti, A.; Silvani, A.; Lesma, G. *Org. Biomol. Chem.* **2016**, *14*, 7768–7776. doi:10.1039/c6ob01359g
12. Bassini, E.; Gazzotti, S.; Sannio, F.; Lo Presti, L.; Sgrignani, J.; Docquier, J.-D.; Grazioso, G.; Silvani, A. *Antibiotics (Basel, Switz.)* **2020**, *9*, 249. doi:10.3390/antibiotics9050249
13. Manenti, M.; Gazzotti, S.; Lo Presti, L.; Molteni, G.; Silvani, A. *Org. Biomol. Chem.* **2021**, *19*, 7211–7216. doi:10.1039/d1ob01303c
14. Chen, J.; Li, J.-H.; Zhu, Y.-P.; Wang, Q.-A. *Org. Chem. Front.* **2021**, *8*, 2532–2536. doi:10.1039/d1qo00186h
15. Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910–6911. doi:10.1021/ja800829y
16. Buesking, A. W.; Bacauanu, V.; Cai, I.; Ellman, J. A. *J. Org. Chem.* **2014**, *79*, 3671–3677. doi:10.1021/jo500300t
17. Dobah, F.; Mazodze, C. M.; Petersen, W. F. *Org. Lett.* **2021**, *23*, 5466–5470. doi:10.1021/acs.orglett.1c01799
18. Qian, Y.-L.; Xia, P.-J.; Li, J.; Zhao, Q.-L.; Xiao, J.-A.; Xiang, H.-y.; Yang, H. *Org. Biomol. Chem.* **2017**, *15*, 8705–8708. doi:10.1039/c7ob02319g
19. Banerjee, P.; Pandey, A. K. *RSC Adv.* **2014**, *4*, 33236–33244. doi:10.1039/c4ra01492h
20. Han, Y.-Y.; Chen, W.-B.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 490–493. doi:10.1021/ol203081x
21. Zhu, W.-R.; Liu, K.; Weng, J.; Huang, W.-H.; Huang, W.-J.; Chen, Q.; Lin, N.; Lu, G. *Org. Lett.* **2020**, *22*, 5014–5019. doi:10.1021/acs.orglett.0c01578
22. Chen, L.-J.; Yu, J.-H.; He, B.; Xie, J.-W.; Liu, Y.-X.; Zhu, W.-D. *J. Org. Chem.* **2020**, *85*, 7793–7802. doi:10.1021/acs.joc.0c00418
23. Shen, X.; Zhou, Y.; Xi, Y.; Zhao, J.; Zhang, H. *Chem. Commun.* **2015**, *51*, 14873–14876. doi:10.1039/c5cc05378a
24. Dotson, J. J.; Bachman, J. L.; Garcia-Garibay, M. A.; Garg, N. K. *J. Am. Chem. Soc.* **2020**, *142*, 11685–11690. doi:10.1021/jacs.0c04760
25. Xu, J.; Li, R.; Xu, N.; Liu, X.; Wang, F.; Feng, X. *Org. Lett.* **2021**, *23*, 1856–1861. doi:10.1021/acs.orglett.1c00260
26. Chen, S.-K.; Ma, W.-Q.; Yan, Z.-B.; Zhang, F.-M.; Wang, S.-H.; Tu, Y.-Q.; Zhang, X.-M.; Tian, J.-M. *J. Am. Chem. Soc.* **2018**, *140*, 10099–10103. doi:10.1021/jacs.8b05386
27. Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488–5508. doi:10.1002/anie.200700612
28. CCDC 2116885 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/structures>.
29. Li, Z.; Zhang, L.; Nishiura, M.; Hou, Z. *ACS Catal.* **2019**, *9*, 4388–4393. doi:10.1021/acscatal.9b00777
30. Ravis, T.; Evans, D. A. Structural and Mechanistic Investigations in Asymmetric Copper(I) and Copper(II) Catalyzed Reactions. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; John Wiley & Sons: New York, NY, USA, 2001; Vol. 50, pp 1–150. doi:10.1002/0471227110.ch1

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