Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202401485
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Diastereo- and Enantioselective Construction of Stereochemical Arrays Exploiting Non-Classical Hydrogen Bonding in Enolborates

Matthew Li[+],[a] Stephan Scheeff[+],[a] Jiahua Chen[+],[b] Ryne C. Johnston,[c] Antonio Rizzo,[a] Elizabeth H. Krenske,*[c] and Pauline Chiu*[a, b]

We report a copper-catalyzed reductive aldol addition to aldehydes and ketones, with pinacolborane as stoichiometric reductant, that results in the generation of stereodefined *syn*-aldol products. Cyclic, acyclic, fused and spirocyclic aldols bearing contiguous stereocenters are obtained with excellent yields and diastereoselectivities. Moreover, enantioselective reactions could be carried out with cycloalkenones to deliver aldols bearing three contiguous stereocenters and with up to 98% ee. Computations reveal that the enolborate intermediate undergoes the *syn*-aldol reaction via a twist-boat transition state that is stabilized by non-classical hydrogen bonding interactions.

Introduction

The robust construction of arrays of stereogenic centers is a major focus of synthetic methodology development. There is a need for achieving the synthesis of stereodiads or triads in a predictable manner with high diastereo- and enantiocontrol. Generating such complexity in one step from abundant and inexpensive materials and reagents is an ongoing challenge for current research.[1]

Among the metals used in organic synthesis, copper is particularly attractive due to its comparatively low cost and low integrated risk.[2–8] As our group has been working on reactions catalyzed by copper, we sought to develop a practical and general approach to stereochemical arrays by expanding the range of copper-mediated transformations.

The aldol reaction is a fundamental carbon-carbon bond forming reaction extensively used in the synthesis of many compounds, including natural products, and particularly, polyketides.[9–11] To date, enolate aldol reactions have been a reliable method for the synthesis of various α- and β-substituted carbonyl compounds.[12–14] Classical aldol reactions used in synthetic chemistry and total synthesis are predominantly based on enolborinate aldol reactions (−OBR_2),[15] organocatalytic approaches (e.g. proline-catalyzed aldol reactions),[16,17] and Mukaiyama-type aldol reactions.[18] In general, the diastereoselectivity of the classical aldol reaction with enolborinates is dependent on the selective generation of either the (*E*)- or (*Z*)-enolate that then undergoes addition to aldehydes to provide *anti*-aldol or *syn*-aldol products, respectively, as rationalized by a Zimmerman-Traxler cyclic transition state.[19] It follows that *syn*-aldol products are not favored from (*E*)-enolates, in particular endocyclic enolates; consequently, access to *syn*-aldol products with dr >6:1 from endocyclic enolates is rare in the literature.[20–29]

In contrast, the aldol reactions of enolborates (−$OB(OR)_2$), first reported by Hoffmann[23–30] and Gennari,[31–33] are *syn*-selective, regardless of the geometry of the enolborate. However, enolborate aldol chemistry has received relatively little attention.[34,35] One obstacle for the development of enolborate aldol chemistry may have been the lack of convenient methods for generating these kinds of boron enolates: they were obtained by oxidation of vinylborates, which limited their synthesis to those derived from a subset of acyclic ketones.[30] Alternatively, enol borylation using the highly sensitive $(RO)_2BCl$, which is not commercially available, did not gain much traction.[31]

As we have previously exploited the mild, copper-catalyzed reduction of enoates to readily access enolborates for Ireland-Claisen rearrangements,[37,38] and for the synthesis of C-boron enolates,[39] we were poised to explore transition metal-catalyzed reductive aldol additions between α,β-unsaturated carbonyl compounds and aldehydes or ketones,[36a,b] a reaction that has also been investigated by Lipshutz and coworkers.[20] In this connection, and concomitant with our studies, Yin reported the generation of enolborates from α,β-unsaturated lactones

[a] M. Li,[+] S. Scheeff,[+] A. Rizzo, P. Chiu
Department of Chemistry and the State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P.R. China
E-mail: pchiu@hku.hk
[b] J. Chen,[+] P. Chiu
Laboratory for Synthetic Chemistry and Chemical Biology Limited, Hong Kong Science Park, Shatin, Hong Kong, P.R. China
[c] R. C. Johnston, E. H. Krenske
School of Chemistry and Molecular Biosciences, Prof. Dr. Elizabeth H. Krenske, The University of Queensland, St Lucia, QLD 4072, Australia
E-mail: e.krenske@uq.edu.au
[+] These authors contributed equally to this work.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202401485

and their *anti*-selective (dr 6:1 to >20:1) intermolecular aldol reactions with ketones (Figure 1a).[40a] Another method published recently described a photo-induced cobalt-catalyzed process, which provided aldol adducts as racemates (Figure 1b).[24] Thomas and co-workers reported the generation of (*Z*)-enolborates by transborylation from enolborane and subsequent aldol.[40b,c]

Herein, we report a general copper-catalyzed 1,4-reduction of α,β-unsaturated carbonyls to generate racemic or enantioenriched enolborates, enabling subsequent intra- or intermolecular aldol reaction with various ketones and aldehydes (Figure 1d). Using this methodology, vicinal stereodiads or triads can be generated with dr as high as 20:1 and, for β-alkylated substrates, with ee's up to 98%. The conditions used are mild, the reaction set-up is simple, and the reagents are commercially available and relatively non-toxic.

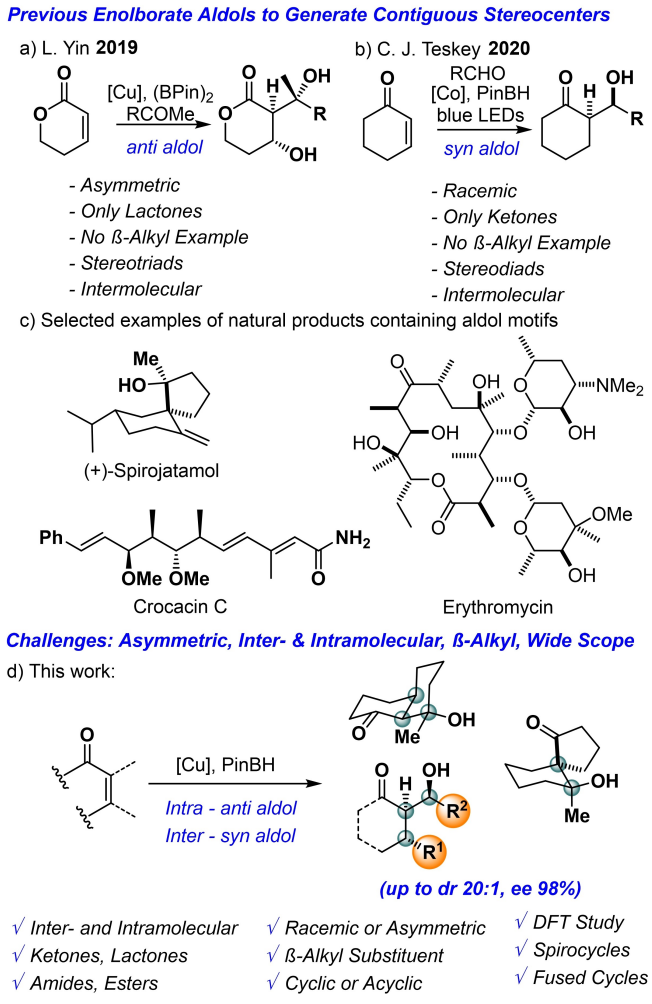


Figure 1. a,b) Features of previously reported aldol reactions involving enolborate intermediates; c) selected examples of natural products that contain aldol motifs;[9–11] d) advancements reported in this paper.

Results and Discussion

Enolborate Selectivity: Theoretical Mechanistic Investigations

It has been reported that the reductive aldol reactions of cyclic enones via enolborinates favoured the *anti*-product, while *syn*-products were obtained via enolborates. We undertook a theoretical study to better understand why different stereoselectivities are displayed in the two types of boron-mediated aldol reactions.[41] Density functional theory (DFT) calculations with M06-2X were performed on the transition states (TSs) for the reactions of the cyclic enolborate **1 b-Bpin** and enolborinate **1 b-BMe$_2$** with benzaldehyde (Figure 2). The computations indicated that the enolborate **1 b-Bpin** favours a twist-boat transition state leading to the *syn* aldol product (**TSA-*syn***).[32,33] This TS is 3 kcal/mol lower in energy than the chair TS leading to the *anti* aldol product (**TSA-*anti***). For the corresponding enolborinate (**1 b-BMe$_2$**), the *syn* and *anti* TSs are both twist-boats. In the *syn* TS (**TSB-*syn***), one of the enolborinate B–Me groups occupies a flagpole position and clashes transannularly with the enol α-hydrogen and the aldehyde hydrogen (dotted lines in Figure 2b), leading to destabilization. The *anti* TS (**TSB-*anti***), which features no such clashes, is 1 kcal/mol lower in energy.

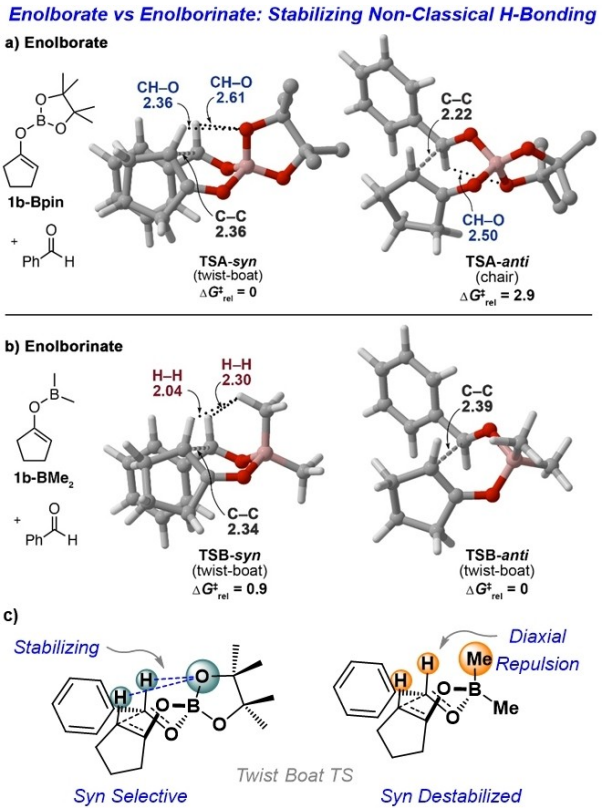


Figure 2. *Syn* and *anti* transition states for the aldol reactions of a) enolborate **1 b-Bpin** and b) enolborinate **1 b-BMe$_2$** with benzaldehyde, computed with M06-2X/6-311+G(d,p) in SMD tetrahydrofuran (distances in Å; $\Delta G^{\ddagger}$ in kcal/mol); c) Schematic depiction of the stabilizing/destabilizing interactions. For clarity, the hydrogens in the methyl groups of the pinacol moiety are not shown.

By contrast, for the enolborate **1b-Bpin**, the flagpole position of the *syn* TS is occupied by a B-OR group, which engages in stabilizing non-classical hydrogen bonding (CH–O) interactions[42] with the enol and aldehyde hydrogens. The 3 kcal/mol difference in energy between the *syn* and *anti* transition states for the enolborate agrees with the empirical observation of high *syn*-diastereoselectivity.

Scope of the Racemic Intermolecular Reaction

To establish a reductive copper-catalyzed aldol reaction, we utilized conditions ($Cu(OAc)_2{\bullet}H_2O$, PPh_3, pinacolborane) previously optimized for reductive Ireland–Claisen rearrangements[37,38] to reduce cyclohexenone **1a** to the corresponding enolborate; efficient coupling with benzaldehyde (Figure 3) then gave **2a** (87%, dr > 20:1). The copper catalyst loading could be decreased to 1.25% to afford the same outcome, but for practicality at our usual experimental scales, we typically employed 5% copper (Figure S1). The high *syn*-selectivity, confirmed by comparison with the reported ^1H and ^{13}C NMR data of **2a**,[43] was consistent with the literature and with our DFT study.

Further explorations on the scope of the reaction found that the copper-catalyzed reductive aldol additions of cyclohexenone (**1a**), cyclopentenone (**1b**), and cycloheptenone (**1c**) with aromatic, primary and secondary aldehydes all proceeded smoothly (Figure 3, **2a**–**j**). It should be noted that α,α-non-branched aliphatic aldehydes are notoriously difficult for aldol reactions due to their tendency to undergo self-condensation under basic conditions; however, this side reaction was successfully suppressed via our reductive approach.

In many cases, simply mixing $Cu(OAc)_2{\bullet}H_2O$, PPh_3 and pinacolborane in the presence of cycloalkenone and aldehyde conveniently afforded the aldol products in good yields. With some aldehydes, such as *p*-nitrobenzaldehyde, the addition of the aldehyde to the reaction mixture after completion of the reductive enolboration of the cycloalkenone avoided the competitive reduction and consumption of the highly electrophilic aldehyde by the *in situ*-generated copper hydride. Previous studies of copper-catalyzed reductive aldol reactions used ketones as electrophiles to bypass this competitive reduction problem. Our results with aldehydes herein demonstrate a more general and diastereoselective aldol addition.[4,44,45]

Unsaturated lactones likewise underwent reductive aldol reactions with aromatic and aliphatic aldehydes with the same high *syn* selectivity (Figure 4, **2k**–**2l**). In comparison, acyclic enones, enoates, and enamides were observed to undergo reductive aldol additions with attenuated diastereoselectivities. Additionally, we observed that chromatographic purification enabled to isolate **2m** and **2o** as single diastereomers (See SI for details).

Our method could also be applied to more challenging β-carboalkoxy substrates. For example, methyl 3-oxocyclohex-1-ene-1-carboxylate (**1h**) was found to undergo chemoselective and diastereoselective reduction aldol addition via a ketone enolborate intermediate (**2p**, dppBz ligand used,[46] dr = 2.6:1 increasing to 11:1 upon partial chromatographic separation, see SI for details). This diastereoselective synthesis from a functionalized substrate, where different and orthogonally reactive moieties are present, highlights the reaction's chemoselectivity. The relative configuration of the *syn* aldol product **2p** was confirmed by crystallographic analysis.

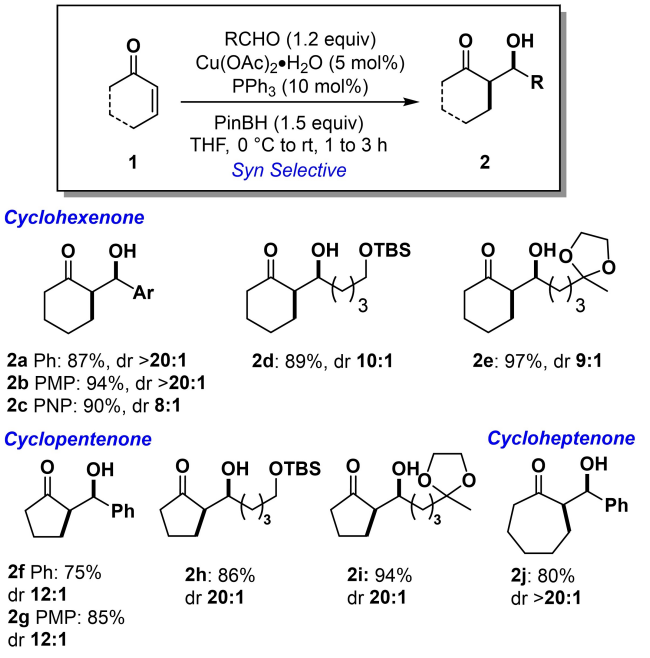


Figure 3. Reductive aldol reactions of α,β-unsaturated carbonyls **1** with several aldehyde partners leading to *syn*-aldol stereodiads (**2**). PMP = *p*-methoxyphenyl, PNP = *p*-nitrophenyl.

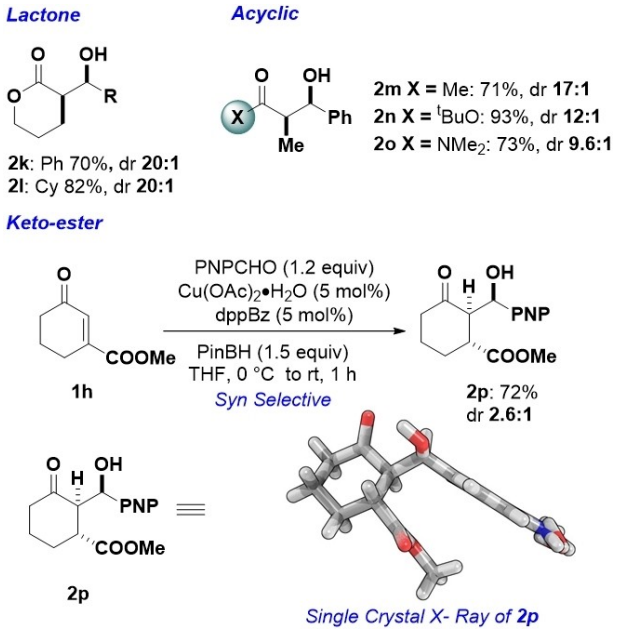
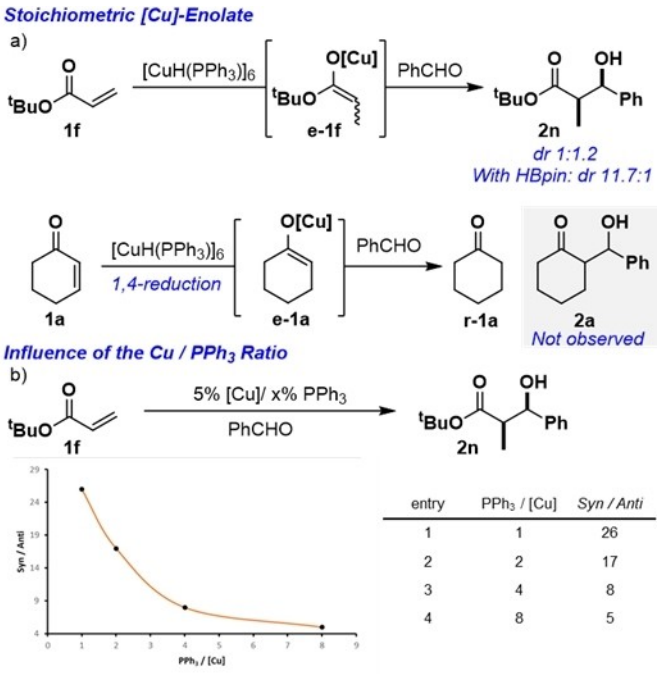


Figure 4. Reductive aldol reactions of α,β-unsaturated lactones and acyclic substrates to *syn*-aldol stereodiads (**2**), including determination of the relative configuration of **2p** by single crystal X-ray analysis. PNP = *p*-nitrophenyl, Cy = cyclohexyl.

Since both (*E*)- and (*Z*)-enolborates undergo *syn*-selective aldol additions,[23–33] we surmise that the lower *syn* selectivities for **2m**–**2o**, derived from acyclic ketone and ester substrates, results from some involvement of direct and less diastereoselective aldol additions occurring via the copper enolates obtained from the copper hydride induced conjugate reduction of the α,β-unsaturated carbonyl substrates.[4,47] In these cases, the direct aldol additions of the copper enolates may be competitive with metathesis with pinacolborane to generate the corresponding enolborates.

To investigate this possibility, we subjected ^{t}Bu-acrylate **1f** to reaction with stoichiometric amounts of Stryker's reagent ($[CuH(PPh_3)]_6$) to generate solely the corresponding copper enolate **e-1f** (Scheme 1a). Quenching with benzaldehyde indeed furnished the aldol adduct **2n** with a much lower selectivity compared to that obtained under the standard conditions (1 : 1.2 vs 11.7 : 1).

On the other hand, while the reduction of cyclic enone **1a** (Scheme 1a) using a stoichiometric amount of $[CuH(PPh_3)]_6$ led to complete 1,4-reduction, addition of benzaldehyde did not produce any aldol product **2a** in the absence of PinBH. This result indicates that the background, non-selective aldol reaction of **e**–**1a** does not occur to any appreciable extent; hence, aldol adducts must be formed via the intermediacy of enolborates, explaining the high diastereoselectivities observed. Moreover, increasing the amount of phosphine, which has been found to promote O-boron to O-copper isomerization,[39] also decreased the *syn* selectivity (Scheme 1b). These data show that the enolborate reaction pathway predominates in the reductive aldol reactions of cyclic carbonyls whereas the acyclic carbonyls can access multiple pathways (Scheme 2).



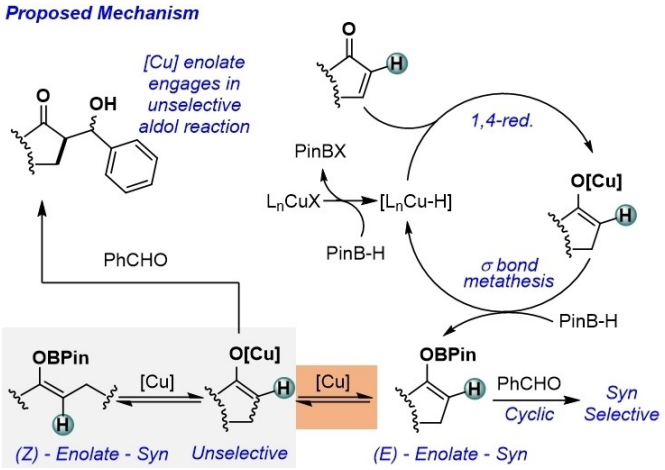
Scheme 1. Investigation of the roles of Cu-enolates: a) stoichiometric reduction of **1f** with $[CuH(PPh_3)]_6$ delivers **2n** with decreased dr compared with the standard conditions; stoichiometric reduction of **1a** with $[CuH(PPh_3)]_6$ delivers cyclohexanone **r-1a** as the only product. b) Increase of the ligand-to-[Cu] ratio decreases the dr (0.1 mmol scale).

Scope of Intramolecular Reactions

To extend the scope of the reaction, we investigated the reductive aldol reaction in an intramolecular setting. Despite strong interest in spirocyclic frameworks, they are surprisingly difficult to synthesize via aldol type reactions;[48–50] a literature search revealing only a few examples.[47,50,51] We reasoned that our reductive approach may offer an advantage for such systems due to the mildness of its conditions and the fact that the trapping of the alcoholates with boron suppresses the retro-aldol reaction.

In the event, under our standard reaction conditions, α-tethered substrates gave spirocyclic aldols **4a-h** in excellent yields through the intermediacy of endocyclic enolborates (Figure 5). Their relative configurations were determined by comparison with characterizations for **4a**, **4c**, **4e**, and **4g** in the literature;[50] we also confirmed the structure of **4f** by X-ray crystallographic analysis. Using the reductive protocol, vicinal stereodiads, of which one is a quaternary carbon, can be readily accessed with excellent *anti*-diastereoselectivity (> 20 : 1 dr). Somewhat surprisingly, no prior syntheses of aldols **4d**, **4f**, or **4h** have previously been reported.

Furthermore, β-tethered substrates **5a** and **5b** (Figure 6a) led to *cis*-fused **6a** and **6b** in good yields. These reactions were facilitated by a higher concentration of PinBH to increase the rate of the metathesis of the copper enolate to the more stable enolborate. In these cases, three contiguous stereocenters were established with a 20 : 1 dr. Notably, no synthesis of **6b** has been reported, and the only reference to **6a** to date had been our previous attempts at reductive aldol cyclizations using stochiometric amounts of Stryker's reagent which afforded **6a** in only 19% yield.[47] In the reactions of substrates like **5** but bearing a shorter or a longer tether to the methyl ketone that could in theory afford five- or seven-membered carbocycles



Scheme 2. Proposed mechanisms for cyclic and acyclic substrates.

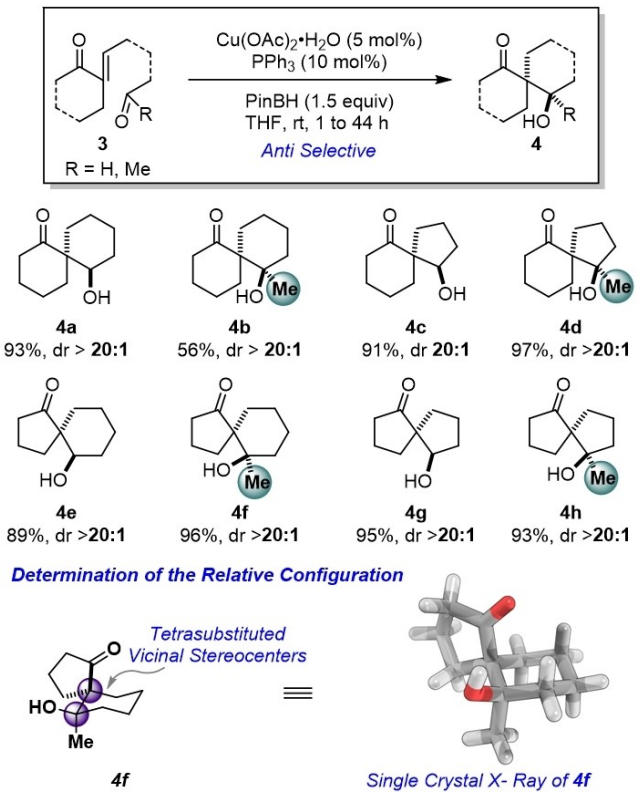


Figure 5. Intramolecular synthesis of spirocyclic aldol products **4**, including determination of the relative configuration of **4 f** by X-ray crystallography.

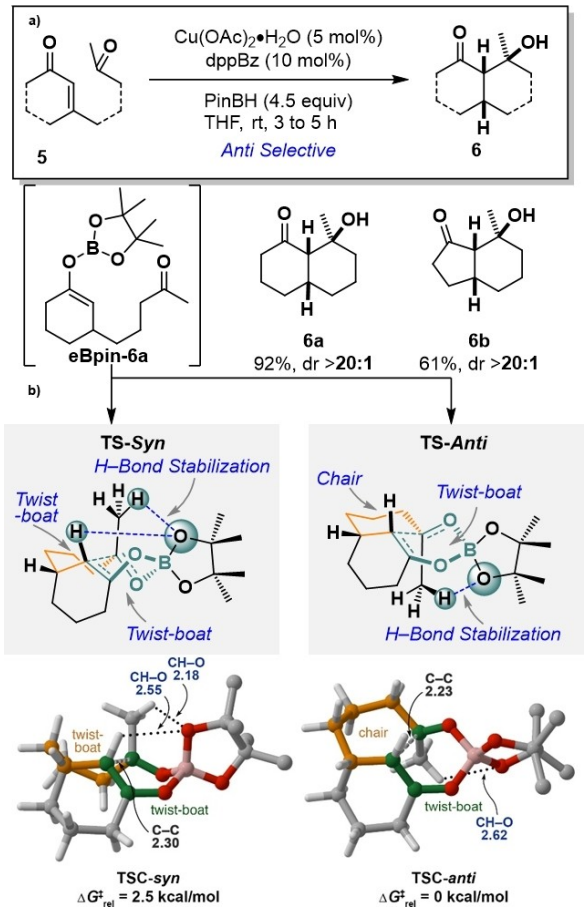


Figure 6. a) Intramolecular synthesis of bicyclic aldol products **6**. b) DFT calculations of the intramolecular enolborate aldol reaction (distances in Å; ΔG^{+} in kcal/mol).

upon reductive cyclization, we only observed 1,4-reduction products and over-reduced products.

In these intramolecular aldol additions, the *anti* stereochemistry of the cyclization products **6** at first glance appears to indicate a return to a Zimmerman–Traxler-like TS. However, computational studies (Figure 6b) indicate that, within the array of reacting atoms (in green), both the *syn* and *anti* TSs have twist-boat ring conformations. The stereoselectivity of the intramolecular reaction depends on the conformation of the adjacent newly-forming six-membered ring (shown in orange). In the *anti* transition state this ring is chair-like, whereas in the *syn* transition state, it adopts a twist-boat conformation. Even with the stabilizing non-classical hydrogen bonding between the enolborate oxygen and hydrogens across the six-membered ring in the *syn*-aldol transition state, the *anti* transition state is still 2.5 kcal/mol lower in energy, consistent with the observed stereochemistry of **6 a**. A similar conformational explanation could perhaps be invoked for the observed *anti* selectivity in the formation of spirocycles **4**.

Scope of the Enantioselective Intermolecular Reaction

Despite the many advances in reductive aldol reactions reported in the literature, there are still few general asymmetric transformations that establish three new contiguous stereocenters with high diastereo- and enantioselectivity in a one-pot aldol process.[6,52] Lipshutz's group first demonstrated that β-substituted cyclohexenones can be reduced with good ee;[20] then by using $(MeO)_2MeSiH$ as the stoichiometric reductant, highly diastereoselective and enantioselective intramolecular reductive aldol reactions of acyclic β,β-disubstituted enones were achieved.[6] The corresponding intermolecular reaction was not successful, however,[20] and an account by the same group remarked specifically that the reductive aldol reaction of β-substituted cyclohexanones remained elusive after extensive investigations.[7]

In general, although enantioselective 1,4-addition can be achieved by using various chiral catalysts,[52–55] the following aldol addition often ensues with low diastereoselectivities. For example, a report by Feringa and colleagues described a highly stereoselective 1,4-addition to cyclohexenone **1 a** (ee 93%); but the following aldol reaction was not diastereoselective (*syn*:*anti*~1 : 2).[52]

To extend our reaction to the sterically congested enones **7 a**–**e**, we used (*R*)-DTBM-SEGPHOS, known to be an efficient ligand for the asymmetric reduction of β,β-disubstituted enones (Figure 7).[6,56] In this reaction, the use of Stryker's reagent as the copper source instead of copper(II) acetate obviated any induction time to generate the active copper hydride, and

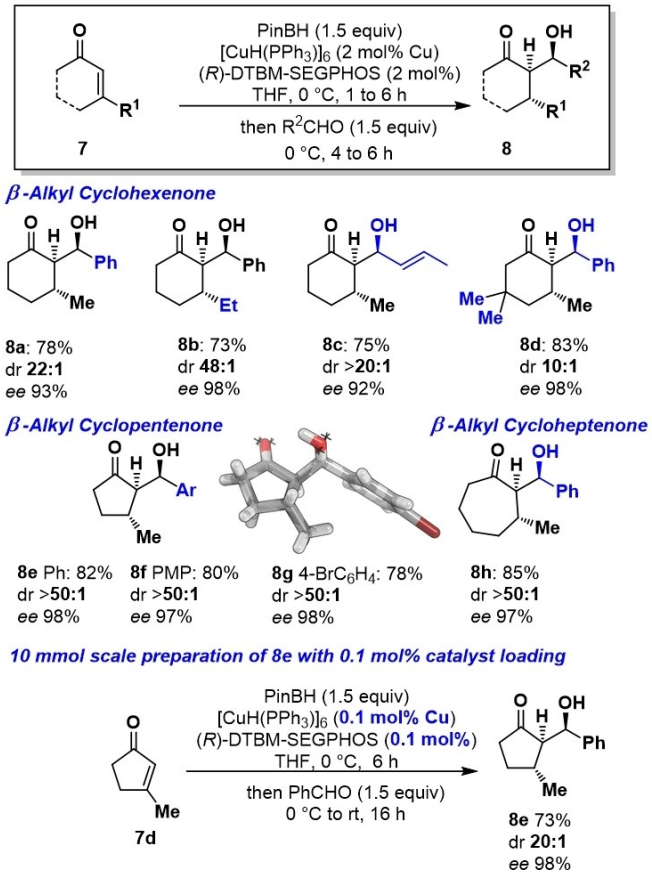


Figure 7. Enantioselective, reductive aldol reactions of β-substituted cycloalkenones **7a-e**, determination of the absolute configuration of **8g** by X-ray crystallography, and a 10 mmol-scale experiment to generate **8e**.

significantly improved the reproducibility as well as the ee to 95%.

Gratifyingly, under the optimized reductive reaction conditions, β-substituted cyclohexenones reacted with aldehydes to afford aldol products **8a**–**8h** bearing three new contiguous stereocenters in excellent ee (up to 98%), and with good diastereoselectivity. Moreover, the reductive aldol reaction of isophorone, which was specifically unreactive under the Lipshutz conditions, was achieved successfully with good yield and ee. Overall, the solution to the putative challenging copper hydride-mediated reductive aldol addition appears to be the use of PinBH, instead of silanes or other alkylboranes. The reaction to generate **8e** was found to proceed smoothly on a larger (10 mmol) scale using 0.1 mmol% of Stryker's reagent.

The *syn*-selectivity achieved with our reductive copper-catalyzed method is complementary to that obtained in alternative approaches involving 1,4-additions by organometallic reagents to **1a** or **1b** which provided aldol products (e.g. **2a**) mainly as *anti*-aldol diastereomers, with varying degrees of diastereoselectivities.[52–55,57–61] Perhaps surprisingly, *syn*-aldol products **8** are rare in literature and a general access to these stereochemically defined compounds in a highly enantioselective and diastereoselective manner has not been reported until now. To the best of our knowledge, this is the first enantioselective and *syn*-selective approach for the construction of this structural motif.[62]

Conclusions

We have shown that the copper(I) hydride-catalyzed reductive additions of cycloalkenones to aromatic and aliphatic aldehydes, in the presence of pinacolborane, are an effective and convenient variant of the aldol reaction that affords good to excellent yields and high *syn*-diastereoselectivities through the intermediacy of endocyclic (*E*)-enolborate intermediates. Intermolecular asymmetric reductive aldol reactions of β-substituted cycloalkenones using this method furnished 2,3-disubstituted cycloalkanones with three contiguous stereocenters in excellent yields and enantioselectivity.

Supporting Information

All synthetic procedures, characterization data, spectroscopic data, supplementary figures, DFT calculations, and crystallographic information are provided in the Supporting Information. The authors have cited additional references within the Supporting Information.[63–88]

Deposition Numbers "https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202401485" 2307017 (for **8g**), 2308408 (for **2p**), 2104221 (for **4f**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe "http://www.ccdc.cam.ac.uk/structures" Access Structures service.

Computational Resources

Computations were performed on the National Facility of the Australian National Computational Infrastructure through the support of the Australian National Computational Merit Allocation Scheme, and on the UQ Research Computing Centre.

Funding Sources

We gratefully acknowledge financial support from the Research Grants Council General Research Fund (HKU 17312222), The State Key Laboratory for Synthetic Chemistry, The Laboratory for Synthetic Chemistry and Chemical Biology under the Health@InnoHK Program launched by the Innovation and Technology Commission, The Government of Hong Kong Special Administrative Region of the People's Republic of China to PC, Australian Research Council (FT120100632 and DP180103047) to EHK.

Acknowledgements

We thank Gordon Man for preliminary experiments. The University of Hong Kong is also acknowledged for a Postdoctoral Fellowship to S.S. under the HKU RAP/PDF Scheme. R.C.J. thanks Oregon State University for a 2013–2014 Graduate Internationalization Grant.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Copper · Enantioselective · Spirocycles · Hydrogen bonding · DFT calculations

[1] K. M. P. Wheelhouse, R. L. Webster, G. L. Beutner, *Org. Process Res. Dev.* **2023**, *27*, 1157.
[2] C. C. Meyer, E. Ortiz, M. J. Krische, *Chem. Rev.* **2020**, *120*, 3721.
[3] H. W. Lam, P. M. Joensuu, *Org. Lett.* **2005**, *7*, 4225.
[4] O. Chuzel, J. Deschamp, C. Chausteur, O. Riant, *Org. Lett.* **2006**, *8*, 5943.
[5] L. Bayeh-Romero, S. L. Buchwald, *J. Am. Chem. Soc.* **2019**, *141*, 13788.
[6] B. Amorelli, J. B. Unger, B. H. Lipshutz, *J. Am. Chem. Soc.* **2008**, *130*, 14378.
[7] B. Lipshutz, *Synlett* **2009**, *4*, 509.
[8] L. Zhang, M. Oestreich, *ACS Catal.* **2021**, *11*, 3516.
[9] B. Schetter, R. Mahrwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7506.
[10] T. P. Stockdale, N. Y. S. Lam, M. J. Anketell, I. Paterson, *Bull. Chem. Soc. Jpn.* **2020**, *94*, 713.
[11] A. Bagchi, H. Hikino, Y. Oshima, *Tetrahedron* **1990**, *46*, 1523.
[12] M. Feng, I. Mosiagin, D. Kaiser, B. Maryasin, N. Maulide, *J. Am. Chem. Soc.* **2022**, *144*, 13044.
[13] T. Amatov, N. Tsuji, R. Maji, L. Schreyer, H. Zhou, M. Leutzsch, B. List, *J. Am. Chem. Soc.* **2021**, *143*, 14475.
[14] L. Lin, K. Yamamoto, H. Mitsunuma, Y. Kanzaki, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2015**, *137*, 15418.
[15] C. J. Cowden, I. Paterson, in *Organic Reactions Vol. 51* (Ed: Leo A. Paquette), John Wiley & Sons, Inc., Hoboken, NJ, USA, **1997**, pp. 1–20.
[16] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[17] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798.
[18] J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109.
[19] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920.
[20] B. H. Lipshutz, P. Papa, *Angew. Chem. Int. Ed.* **2002**, *41*, 4580.
[21] K. Yoshida, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2003**, *68*, 1901.
[22] T. Shiomi, T. Adachi, J.-i. Ito, H. Nishiyama, *Org. Lett.* **2009**, *11*, 1011.
[23] R. W. Hoffmann, K. Ditrich, S. Froech, D. Cremer, *Tetrahedron* **1985**, *41*, 5517.
[24] F. Beltran, E. Bergamaschi, I. Funes-Ardoiz, C. J. Teskey, *Angew. Chem. Int. Ed.* **2020**, *59*, 21176.
[25] K. Hayashi, H. Kogiso, S. Sano, Y. Nagao, *Synlett* **1996**, *1996*, 1203.
[26] R. Mahrwald, *Chem. Ber.* **1995**, *128*, 919.
[27] M. Nakajima, T. Yokota, M. Saito, S. Hashimoto, *Tetrahedron Lett.* **2004**, *45*, 61.
[28] R. A. Flowers, X. Xu, C. Timmons, G. Li, *Eur. J. Org. Chem.* **2004**, 2988.
[29] A. Yanagisawa, Y. Nakatsuka, K. Asakawa, H. Kageyama, H. Yamamoto, *Synlett* **2001**, *69*.
[30] R. W. Hoffmann, K. Ditrich, *Tetrahedron Lett.* **1984**, *25*, 1781.
[31] C. Gennari, S. Cardani, L. Colombo, C. Scolastico, *Tetrahedron Lett.* **1984**, *25*, 2283.
[32] C. Gennari, R. Todeschini, M. G. Beretta, G. Favini, C. Scolastico, *J. Org. Chem.* **1986**, *51*, 612.
[33] A. Bernardi, A. M. Capelli, C. Gennari, J. M. Goodman, I. Paterson, *J. Org. Chem.* **1990**, *55*, 3576.
[34] G. P. Boldrini, L. Lodi, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Organomet. Chem.* **1987**, *336*, 23.
[35] T. Basile, S. Biondi, G. P. Boldrini, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1025.
[36] a) C. C. Meyer, E. Ortiz, M. J. Krische, *Chem. Rev.* **2020**, *120*, 3721; b) T.-l. Li, PhD thesis, University of Hong Kong, **2018**, 10.5353/th_991044040581703414.
[37] K. C. Wong, E. Ng, W.-T. Wong, P. Chiu, *Chem. Eur. J.* **2016**, *22*, 3709.
[38] S. Guo, K. C. Wong, S. Scheeff, Z. He, W. T. K. Chan, K.-H. Low, P. Chiu, *J. Org. Chem.* **2021**, *87*, 429.
[39] E. W. H. Ng, K.-H. Low, P. Chiu, *J. Am. Chem. Soc.* **2018**, *140*, 3537.
[40] a) Q. Zhang, X. Jia, L. Yin, *Tetrahedron* **2019**, *75*, 1676; b) A. Moreno González, K. Nicholson, N. Llopis, G. S. Nichol, T. Langer, A. Baeza, S. P. Thomas, *Angew. Chem. Int. Ed.* **2022**, *61*, e202209584; c) K. Nicholson, T. Langer, S. P. Thomas, *Org. Lett.* **2021**, *23*, 2498.
[41] J. M. Goodman, R. S. Paton, *Chem. Commun.* **2007**, *2124*.
[42] R. C. Johnston, P. H.-Y. Cheong, *Org. Biomol. Chem.* **2013**, *11*, 5057.
[43] T. Kanemitsu, A. Umehara, M. Miyazaki, K. Nagata, T. Itoh, *Eur. J. Org. Chem.* **2011**, *993*.
[44] H. Suzuki, K. Yoneoka, S. Kondo, T. Matsuda, *Chem. Eur. J.* **2022**, *28*, e2021042.
[45] A. Welle, S. Díez-González, B. Tinant, S. P. Nolan, O. Riant, *Org. Lett.* **2006**, *8*, 6059.
[46] B. A. Baker, V. Bošković, B. H. Lipshutz, *Org. Lett.* **2008**, *10*, 289.
[47] P. Chiu, C. P. Szeto, Z. Geng, K. F. Cheng, *Tetrahedron Lett.* **2001**, *42*, 4091.
[48] K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, G. Tsuchihashi, *J. Am. Chem. Soc.* **1986**, *108*, 3827.
[49] H. Suemune, K. Maeda, K. Kato, K. Sakai, *J. Chem. Soc. Perkin Trans. 1* **1994**, *3441*.
[50] T. Toru, T. Wakayama, Y. Watanabe, Y. Ueno, *Phosphorus Sulfur Silicon Relat. Elem.* **1992**, *67*, 253.
[51] K. Inanaga, M. Wollenburg, S. Bachman, N. J. Hafeman, B. M. Stoltz, *Chem. Sci.* **2020**, *11*, 7390.
[52] B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620.
[53] A. Alexakis, P. Garcia, N. Germain, S. Woodward, *Synlett* **2015**, *26*, 901.
[54] A. Mandoli, L. A. Arnold, A. H. M. de Vries, P. Salvadori, B. L. Feringa, *Tetrahedron* **2001**, *12*, 1929.
[55] K. C. Nicolaou, W. Tang, P. Dagneau, R. Faraoni, *Angew. Chem. Int. Ed.* **2005**, *44*, 3874.
[56] B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa, A. A. Lover, *Org. Lett.* **2004**, *6*, 1273.
[57] M. Suzuki, T. Kawagishi, A. Yanagisawa, T. Suzuki, N. Okamura, R. Noyori, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1299.
[58] M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999.
[59] E. Keller, J. Maurer, R. Naasz, T. Schader, A. Meetsma, B. L. Feringa, *Tetrahedron* **1998**, *9*, 2409.
[60] N. Arisetti, O. Reiser, *Org. Lett.* **2014**, *17*, 94.
[61] M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Tetrahedron Lett.* **1996**, *37*, 5141.
[62] This asymmetric method can also be extended to other types of substrates. For example, synthesis of 6a using chiral ligand (R)-DTBM-SEGPHOS induced a good enantioselectivity (97% ee), but the overall yield was poor (27%) with recovery of large amounts of simple reduction product (see SI for details).
[63] P. Chiu, Z. Li, K. C. M. Fung, *Tetrahedron Lett.* **2003**, *44*, 455.
[64] A. P. Dieskau, B. Plietker, *Org. Lett.* **2011**, *13*, 5544.
[65] M. Peña-López, M. M. Martínez, L. A. Sarandeses, J. P. Sestelo, *Org. Lett.* **2010**, *12*, 852.
[66] S. A. Snyder, D. S. Treitler, A. P. Brucks, W. Sattler, *J. Am. Chem. Soc.* **2011**, *133*, 15898.
[67] K. J. Frankowski, J. E. Golden, Y. Zeng, Y. Lei, J. Aubé, *J. Am. Chem. Soc.* **2008**, *130*, 6018.
[68] T. Ogura, T. Usuki, *Tetrahedron* **2013**, *69*, 2807.
[69] V. Rerat, G. Dive, A. A. Cordi, G. C. Tucker, R. Bareille, J. Amédée, L. Bordenave, J. Marchand-Brynaert, *J. Med. Chem.* **2009**, *52*, 7029.
[70] J. R. Backes, U. Koert, *Eur. J. Org. Chem.* **2006**, *2777*.
[71] K. M. Peese, D. Y. Gin, *Chemistry* **2008**, *14*, 1654.
[72] S. Yamada, S. Karasawa, Y. Takahashi, M. Aso, H. Suemune, *Tetrahedron* **1998**, *54*, 15555.

[73] K. Hayashi, E. Kujime, H. Katayama, S. Sano, Y. Nagao, *Chem. Pharm. Bull.* **2007**, *55*, 1773.
[74] S. Kotani, S. Aoki, M. Sugiura, M. Nakajima, *Tetrahedron Lett.* **2011**, *52*, 2834.
[75] D. Acetti, E. Brenna, C. Fuganti, F. G. Gatti, S, Serra, *Eur. J. Org. Chem.* **2010**, *142*.
[76] A. Kamimura, H. Mitsudera, S. Asano, S. Kidera, A. Kakehi, *J. Org. Chem.* **1999**, *64*, 6353.
[77] S. E. Denmark, B. D. Griedel, D. M. Coe, M. E. Schnute, *J. Am. Chem. Soc.* **1994**, *116*, 7026.
[78] G. R. Dake, M. D. B. Fenster, M. Fleury, B. O. Patrick, *J. Org. Chem.* **2004**, *69*, 5676.
[79] G. R. Dake, M. D. B. Fenster, M. Fleury, B. O. Patrick, CCDC 250054: Experimental Crystal Structure Determination, **2005**. https://doi.org/10.5517/CC8D683..
[80] P. Chiu, C.-P. Szeto, Z. Geng, K.-F. Cheng, *Org. Lett.* **2001**, *3*, 1901.
[81] J. Nokami, T. Mandai, H. Watanabe, H. Ohyama, J. Tsuji, *J. Am. Chem. Soc.* **1989**, *111*, 4126.
[82] Y. Q. Tu, C. A. Fan, S. K. Ren, A. S. C, Chan, *J. Chem. Soc. Perkin Trans. 1* **2000**, *3791*.
[83] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Jr. Montgomery, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, *Gaussian 16 Revision C.01*, Gaussian Inc., Wallingford CT, USA **2016**.
[84] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
[85] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.
[86] Y. Zhao, D. G. Truhlar, *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813.
[87] G. M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3–8.
[88] G. M. Sheldrick, *Acta Cryst.* **2015**, *C71*.

Manuscript received: April 17, 2024
Accepted manuscript online: June 3, 2024
Version of record online: July 26, 2024