

Enantioselective Carboetherification/Hydrogenation for the Synthesis of Amino Alcohols via a Catalytically Formed Chiral Auxiliary

Luca Buzzetti,[‡] Mikus Puriņš,[‡] Phillip D. G. Greenwood,[‡] and Jerome Waser*



Cite This: *J. Am. Chem. Soc.* 2020, 142, 17334–17339



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ABSTRACT: Chiral auxiliaries and asymmetric catalysis are the workhorses of enantioselective transformations, but they still remain limited in terms of either efficiency or generality. Herein, we present an alternative strategy for controlling the stereoselectivity of chemical reactions. Asymmetric catalysis is used to install a transient chiral auxiliary starting from achiral precursors, which then directs diastereoselective reactions. We apply this strategy to a palladium-catalyzed carboetherification/hydrogenation sequence on propargylic amines, providing fast access to enantioenriched chiral amino alcohols, important building blocks for medicinal chemistry and drug discovery. All stereoisomers of the product could be accessed by the choice of ligand and substituent on the propargylic amine, leading to a stereodivergent process.

Currently, most enantioselective transformations rely on two strategies: (i) the use of chiral auxiliaries¹ and (ii) asymmetric catalysis.² The former allows the development of general and robust processes, but requires stoichiometric amounts of enantiopure precursors and multistep procedures. By contrast, asymmetric catalysis relies only on substoichiometric amounts of enantiopure molecules, but it generally requires an intensive optimization at the expense of robustness and generality. To overcome these limitations, we envisioned a catalytic enantioselective method, which would introduce a chiral auxiliary on the substrate from a cheap nonchiral tether in a synthetic useful step (Scheme 1A). This process would require only a catalytic amount of enantiopure species while providing a robust platform for further diastereoselective functionalizations, benefiting from the best aspects of the two traditional strategies. To the best of our knowledge, such an approach has not yet been realized, although different methods for improving asymmetric synthesis have been developed. A seminal work based on the formation of chiral amins is the “self-reproduction of chirality” reported by Seebach for the stereoselective synthesis of amino acids. In this work, the existing stereocenter on the amino acid first controls the diastereoselective formation of the amination by condensation with an aldehyde. The latter then shields one face of the enolate.^{3,4} As another example based on an internal chirality transfer, Maulide and co-workers recently reported a redox-neutral coupling of alkenes and aldehydes via a “catch–release” tethering approach (Scheme 1B).⁵ However, the resulting functional group (a ketone) remains in the product. Other researchers have worked on the concept of “transient chiral auxiliaries/tethers”, which are easy to install and remove.^{6–10} For example, Beauchemin and co-workers have used chiral aldehydes in substoichiometric amounts for the Cope-type hydroamination of allyl amines (Scheme 1C).¹¹ However, the

scope of these transformations remains limited, and auxiliaries available from the chiral pool are generally required.

To implement our concept, we considered the palladium-catalyzed carboetherification of propargylic amines,¹² based on the use of trifluoroacetaldehyde-derived tethers (Scheme 1D).^{13–15} The stereocenter formed in this step could direct a subsequent functionalization of the double bond, acting *de facto* as a chiral auxiliary. The rigid nature of the oxazolidine scaffold containing the stereocenter should secure a high level of diastereoselectivity to the following transformations.

Concerning the following diastereoselective functionalization, we found the hydrogenation of the formed double bond particularly attractive. By comparison, the enantioselective hydrogenation of alkyl- or heteroatom-tetrasubstituted olefins is highly challenging, with only few limited catalytic enantioselective systems reported.^{16–18} After removal of the tether molecule, this process would provide amino alcohols, key building blocks in synthetic and medicinal chemistry, which have been the focus of intensive methodology development recently.^{19–26} In particular, the diaryl-substituted amino alcohols obtained using this strategy can be found in antidepressants^{27,28} and have served as intermediates for the synthesis of antimycotic, antibacterials²⁹ and antiviral molecules.^{30,31} However, the selective synthesis of one of the four possible stereoisomers of the amino alcohols generally requires multistep processes.

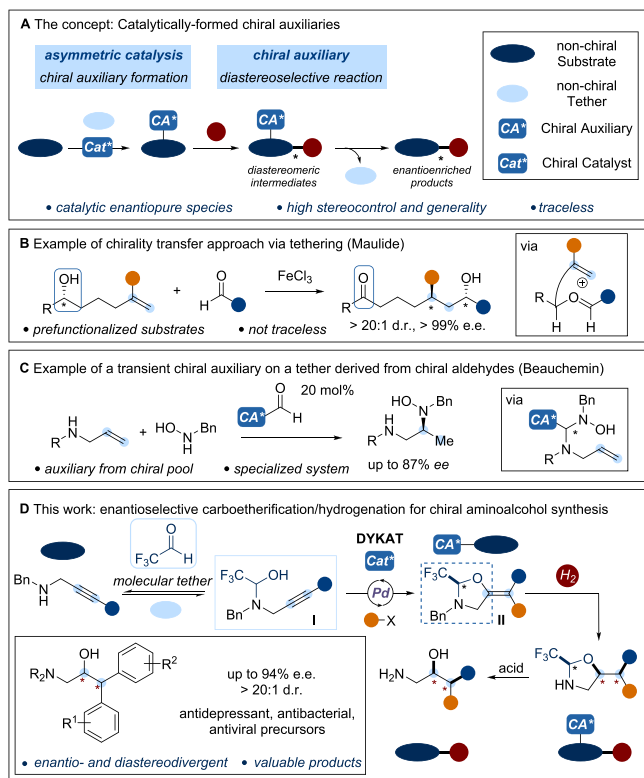
To make this process successful, an enantioselective carboetherification step had to be developed. The reversible

Received: September 1, 2020

Published: October 2, 2020



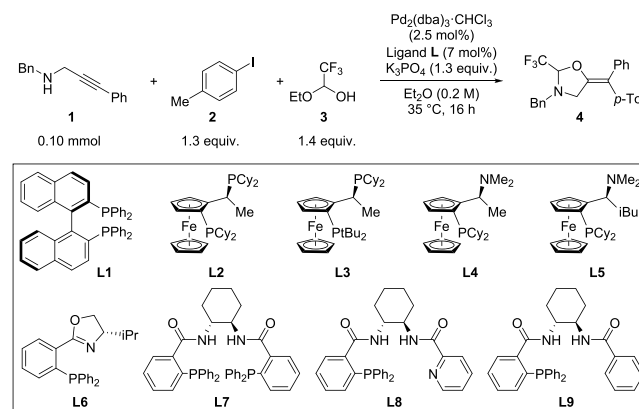
Scheme 1. (A) Our Concept: Catalytically Formed Chiral Auxiliaries; (B) Chirality Transfer via Tethering; (C) Transient Chiral Auxiliaries Introduced from Chiral Pool; (D) Implementation for the Stereodivergent Synthesis of Amino Alcohols



formation of the hemiaminal **I** from the propargylic amine prevents asymmetric induction at this stage (see [Supporting Information](#) (SI), section E for more details). Therefore, a dynamic kinetic asymmetric transformation (DYKAT) needs to take place: in the presence of a chiral catalyst, one enantiomer of **I** should react preferentially to give oxazolidine **II** enantioselectively. Although palladium-catalyzed DYKATs have been reported,³² the envisaged process is highly challenging, due to the large distance between the chiral metal complex and the stereocenter. To the best of our knowledge, such a DYKAT process has never been realized in the palladium-catalyzed functionalization of alkynes. If successful, the selection of the substitution pattern on the alkyne and on the aryl electrophile, together with the choice of the suitable enantiomer of the chiral ligand on the palladium catalyst would provide a simple enantio- and diastereodivergent access to all four stereoisomers of the amino alcohol. This is especially attractive for medicinal chemistry, as each stereoisomer may have different bioactivity, and the development of stereodivergent methods has been the topic of intensive research in asymmetric catalysis recently.^{33–35}

We tested the feasibility of our plan by examining the palladium-catalyzed tethered carboetherification of the readily available propargylic amine **1** with iodotoluene **2** to access tetrasubstituted olefin **4** bearing a chiral oxazolidine fragment (Table 1). 1-Ethoxy trifluoroethanol **3**, a commercially available ethyl hemiacetal of trifluoroacetaldehyde, was chosen as the electrophilic molecular tether, and Pd₂(dba)₃·CHCl₃, as the palladium source.¹² We first focused on the identification of a suitable ligand that could secure a high level of

Table 1. Optimization Studies



entry	Conditions	4 yield (%) ^a	e.e. (%)
1	Ligand L1, L2 or L3	<5	–
2	Ligand L4	44	20
3	Ligand L5	33	30
4	Ligand L6	72	40
5	Ligand L7	49	64
6	Ligand L8	45	74
7	Ligand L9	>95	90
8	L9, EtOAc instead of Et ₂ O	80	84
9	L9, MTBE instead of Et ₂ O	89	89
10	L9, Toluene instead of Et ₂ O	91	91
11 ^b	L9, 0.40 mmol of 1	>95	94

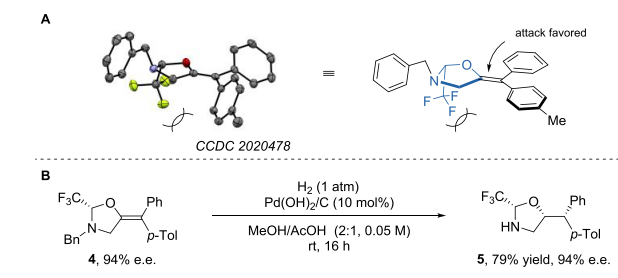
^aNMR yields. ^bReaction performed using 1.25 mol % of Pd₂(dba)₃·CHCl₃ and 3.5 mol % of (S,S)-ligand.

stereoreduction in the process (for details, see [SI](#), section C). Commonly used bidentate BINAP **L1** and Josiphos ligands **L2** and **L3** were not competent for this reaction (entry 1). The P,N ligands **L4** and **L5**, derived from the corresponding Ugi's amines,³⁶ delivered **4** in moderate yield and enantiomeric excess (entries 2 and 3), nevertheless demonstrating that a DYKAT was possible. However, higher asymmetric induction could not be achieved with this class of ligands. The P,N ligand S-*i*PrPhox **L6** yielded the desired product in 72% yield and 40% e.e. (entry 4). Promising results were obtained evaluating the Trost type ligands, commonly used for palladium catalyzed asymmetric allylation reactions.^{37,38} In particular, the commercially available DACH-phenyl Trost ligand **L7** delivered product **4** in 49% yield and 64% e.e. (entry 5). Having in mind the previous positive results obtained with P,N ligands, we substituted the 2-(PPh₂)-aryl fragment with a 2-pyridine.³⁹ This change increased the e.e. to 74% (entry 6). Surprisingly, the best results were finally obtained employing the benzamide derived **L9** lacking a second strongly coordinating site, which delivered quantitatively **4** with 90% e.e. (entry 7). To the best of our knowledge, ligand **L9** has been reported only twice in the literature,^{40,41} and it was not suitable for imparting high stereocontrol, as two strong coordinating sites were required for asymmetric induction. We developed a robust and operationally simple route for accessing both enantiomers of **L9** on multigram scale ([SI](#), section B4). Demonstrating the process's robustness, the reaction could be performed in more "industrially preferred" solvents⁴² (ethyl acetate, methyl *tert*-butyl ether and toluene, entries 8, 9 and 10), without loss of yield and enantioselectivity, except for ethyl acetate (entry 8). Finally, the reaction could be scaled up to a 0.40 mmol scale, reducing the catalyst and ligand loading to 1.25 and 3.5 mol %,

resulting in an improved stereoselectivity of 94% e.e. (entry 11).

The structure of **4**, obtained by X-ray single-crystal analysis (Scheme 2A), shows that the trifluoromethyl group is

Scheme 2. (A) X-ray Crystal Structure of the Product 4; (B) Optimized Conditions for the Diastereoselective Hydrogenation



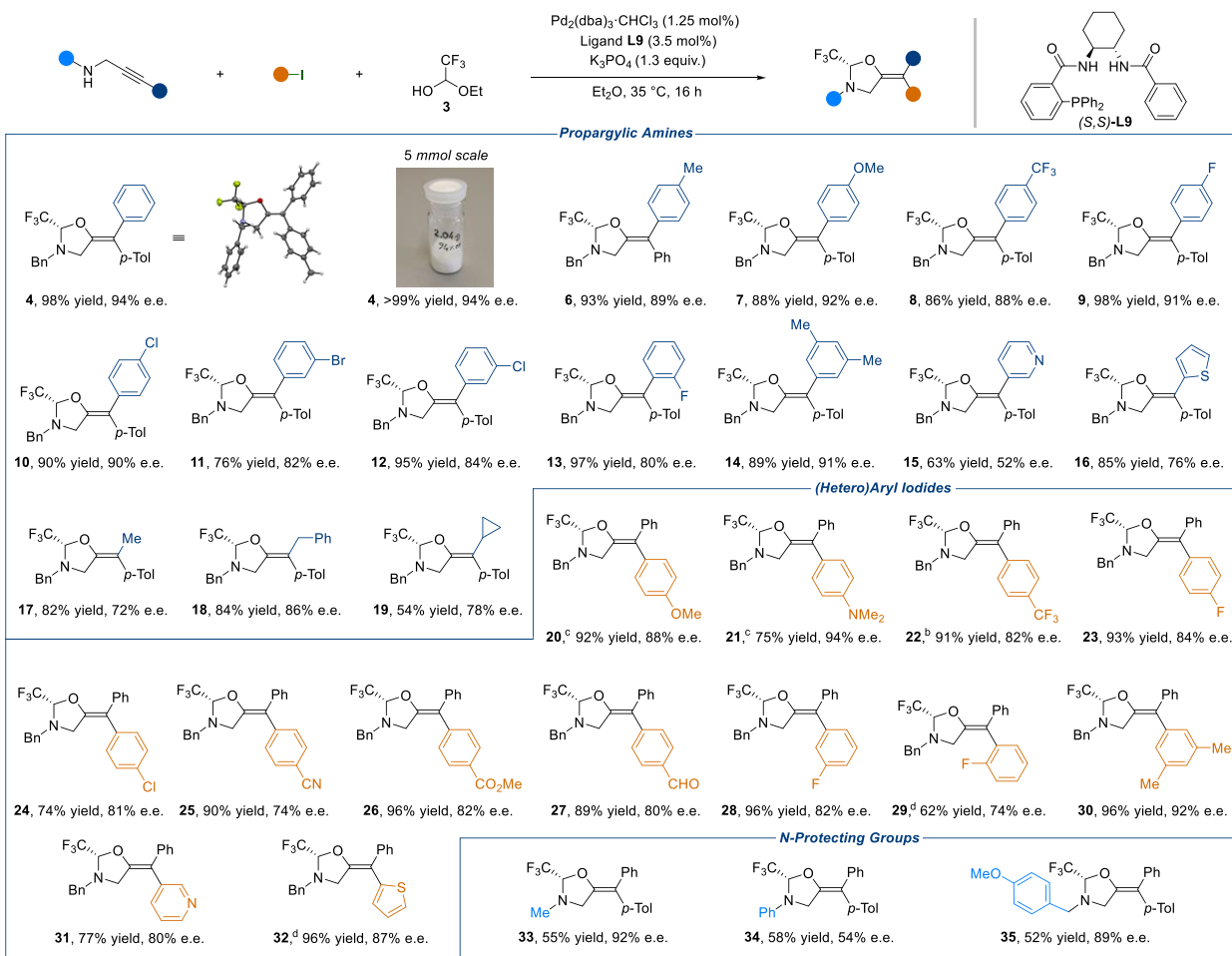
efficiently shielding one of the two enantiotopic faces of the olefin, setting the stage for the stereospecific hydrogenation. Indeed, when we submitted **4** to classical conditions for heterogeneous hydrogenation using Pearlman's catalyst,⁴³ the desired hydrogenated product **5** was obtained as a single

diastereoisomer in 79% yield and 94% e.e. (Scheme 2B). The use of Pearlman's catalyst also allowed simultaneous removal of the benzyl protecting group.

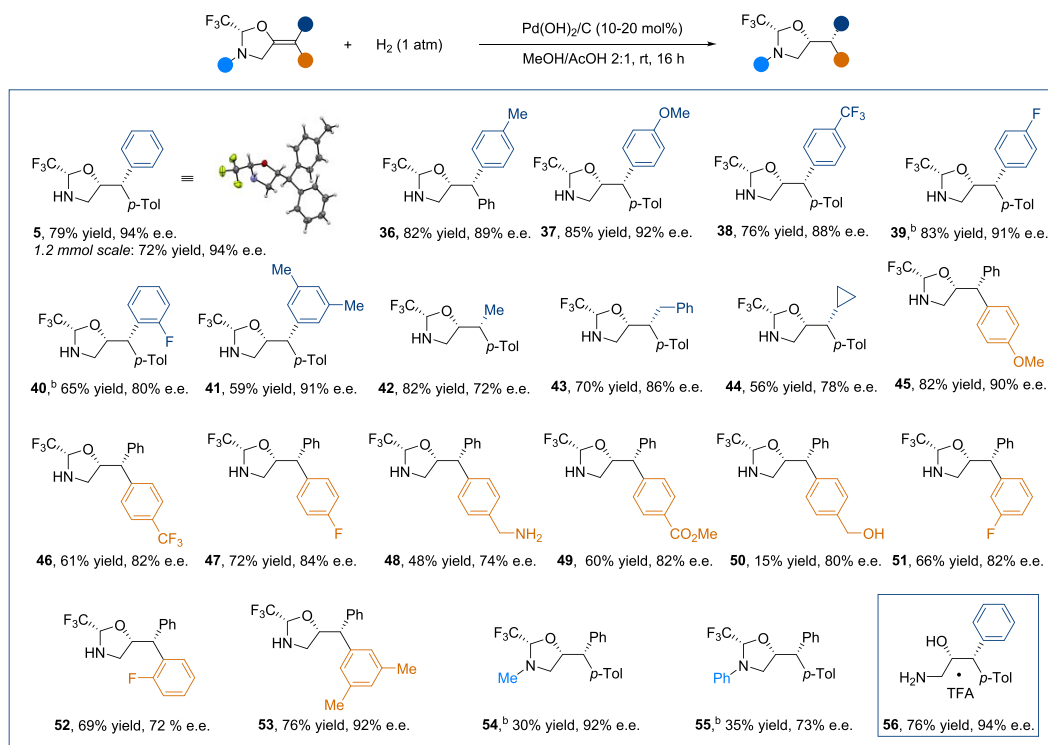
Various aryl propargylic amines were well tolerated in the reaction, regardless of the position of the substituents on the phenyl ring, as well as their electronic and steric properties (Scheme 3, 4, 6–14). The geometry of the olefin can be switched by just exchanging the aryl group on the alkyne and the aryl iodide (**4** vs **6**). The reaction tolerates heterocycles such as pyridine and thiophene on the alkyne, although an erosion of the enantioselectivity was observed (**15** and **16**). Alkyl propargylic amines delivered products **17–19** bearing a methyl, a benzyl, and a cyclopropyl group. The reaction could be performed on a 5 mmol scale providing 2.0 g of **4** (quantitative yield) without erosion of the optical purity. The absolute configuration of the products were assigned by X-ray analysis of **4**, confirming in addition that the aryl group coming from the iodide is incorporated in *trans* position to the oxygen.

The investigation of the scope of the iodoarene showed that numerous synthetically useful functional groups, including ethers, amines, halogens, esters, nitriles or aldehydes, are well tolerated independently from their electronic and steric properties or position on the benzene ring (**20–30**). 2-Iodothiophene and 3-iodopyridine delivered products **31** and

Scheme 3. Scope of the Enantioselective Carboetherification^a



^aReactions performed on a 0.40 mmol scale using 1.3 equiv of aryl iodide and 1.4 equiv of 1-ethoxy trifluoroethanol (**3**). Isolated yields and HPLC enantiomeric excess are given. ^bDichloroethane (DCE) instead of Et₂O. ^cUsing 2.5 mol % of Pd₂(dba)₃·CHCl₃ and 7 mol % of ligand. ^dDCE at 60 °C.

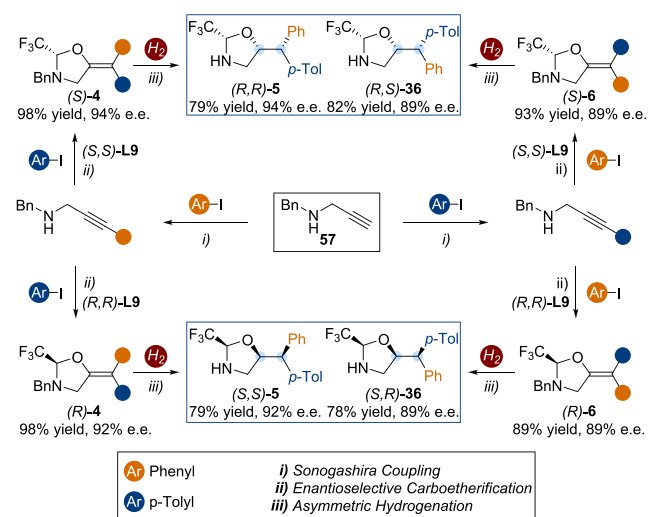
Scheme 4. Scope of the Stereoselective Hydrogenation^a

^aReactions performed on a 0.2 mmol scale using $\text{Pd}(\text{OH})_2/\text{C}$ (~20 wt %). Isolated yields and HPLC enantiomeric excess are given. Product **56** was obtained after treating **5** with $\text{TsOH}\cdot\text{H}_2\text{O}$ (7 equiv) in a 2:1 THF/ H_2O mixture at room temperature for 16 h, the trifluoroacetate salt was obtained after purification by reversed phase preparative HPLC. ^b Pd/C (~5 wt %) was used instead of $\text{Pd}(\text{OH})_2/\text{C}$.

32 in good yields. Finally, *N*-methyl, *N*-phenyl and *N*-*para*-methoxybenzyl (PMB) propargyl amines delivered products **33–35** in 52–58% yield and 54–92% e.e.

The obtained enantioenriched tetrasubstituted olefins were then submitted to the optimized conditions for the diastereoselective hydrogenation (Scheme 4). Products **36–55** were all obtained as single diastereoisomers, confirming the robustness of our approach. Scale-up was straightforward and compound **5** could be obtained in 72% yield on 1.2 mmol scale without erosion of stereoselectivity. Heterocycles and functional groups containing coordinating N or S atoms and chlorides were not tolerated in the hydrogenation step (for details, see SI, Section D5). The nitrile and the carbonyl group within **25** and **27** were reduced to the corresponding amine **48** and alcohol **50**.⁴⁴ Interestingly, **5**, **36**, **45**, **46**, **47** and **54** are precursors of bioactive compounds with antidepressive activity,^{27,28} while the amino alcohols derived from **36** and **47** are intermediates for the synthesis of patented antiviral drugs candidates.³⁰ Remarkably, our method provides a high level of asymmetric induction even in the presence of sterically and electronically similar aryl substituents on the olefin, thus overcoming a common obstacle in the development of catalytic asymmetric reactions. Finally, to confirm the traceless nature of our strategy, we performed a mild acidic hydrolysis of the hemiaminal in **5**. The enantioenriched amino alcohol **56** was obtained in 76% yield without loss in optical purity.

We then demonstrated that this strategy provides a simple stereodivergent access to the four possible stereoisomers of chiral diaryl aminoalcohols by a judicious selection of the substrates and the ligands (Scheme 5). Starting from the benzyl propargyl amine **57**, a sequence of (i) Sonogashira coupling, (ii) enantioselective carboetherification and (iii)

Scheme 5. Diastereo- and Enantiodivergent Access to Chiral Aminoalcohol Precursors^a

^aSee SI for detailed reaction conditions.

diastereoselective hydrogenation leads to all the stereoisomers of the desired products **5** and **36**. Permuting the iodoarenes in the cross-coupling and in the carboetherification steps allows the tuning of the *E,Z* geometry of the double bond. This selective process, combined with the choice of the enantiomer of the ligand, and the diastereoselectivity of the hydrogenation provide a selective access to the four stereoisomers of the diaryl amino alcohol precursors.

In summary, we have developed an innovative strategy to control the stereoselectivity of asymmetric transformations.⁴⁵ Our approach first capitalizes on the tools of asymmetric catalysis to forge a chiral oxazolidine from broadly available propargylic amines. This stereogenic element is then used to control the selectivity of the asymmetric hydrogenation of the tetrasubstituted double bond, giving access to valuable chiral amino alcohol precursors. The key for success was the first use of a “truncated” monophosphine Trost-type ligand to induce high enantioselectivity in an unprecedented DYKAT process. Combined with a Sonogashira cross-coupling, our approach gives a stereodivergent access to the four stereoisomers of protected diaryl amino alcohols in high yield and enantioselectivity. New opportunities for the design and development of asymmetric functionalizations of olefins can be expected based on the combination of the enantioselective introduction of a transient chiral auxiliary followed by a diastereoselective transformation. Such processes are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c09177>.

Experimental procedures and characterization data for starting materials, ligands and products; proposed reaction mechanism; copy of HPLC and NMR spectra (PDF)

Crystallographic data for the product 4 (CIF)

Crystallographic data for the product 5 (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Jerome Waser – Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL, 1015 Lausanne, Switzerland; orcid.org/0000-0002-4570-914X; Email: jerome.waser@epfl.ch

Authors

Luca Buzzetti – Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL, 1015 Lausanne, Switzerland

Mikus Puriņš – Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL, 1015 Lausanne, Switzerland

Phillip D. G. Greenwood – Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL, 1015 Lausanne, Switzerland

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/jacs.0c09177>

Author Contributions

[‡]L.B., M.P., and P.D.G.G. contributed equally.

Notes

The authors declare no competing financial interest. Crystallographic data for the product 4 and 5 have been deposited at the Cambridge Crystallographic Data Centre, accession numbers CCDC 2020478 and 2020479, respectively. Raw HPLC, NMR, MS and IR data is available at <https://doi.org/10.5281/zenodo.4046256>.

■ ACKNOWLEDGMENTS

This work is supported by the European Research Council (ERC Consolidator Grant SeleCHEM, No. 771170 and EPFL). We thank Dr. R. Scopelliti from ISIC at EPFL for X-ray analysis. This publication was created as part of NCCR Catalysis, a National Centre of Competence in Research funded by the Swiss National Science Foundation.

■ ABBREVIATIONS

Me, Methyl; Bu, Butyl; Pr, Propyl; Cy, Cyclohexyl; Ph, Phenyl; Bn, Benzyl; *p*-Tol, *p*-Tolyl; EtOAc, Ethyl acetate; MTBE, Methyl *tert*butyl ether; Et₂O, Diethyl ether; MeOH, Methanol; AcOH, Acetic acid; dba, Dibenzylideneacetone.

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- (44) Product **55** was obtained with higher *e.e.* compared to its precursor **34**. The reasons for this surprising result are unclear at this stage. As **34** was not fully soluble under these conditions, a plausible explanation would be a lower solubility of the racemate salt, leading to a chiral resolution during hydrogenation.
- (45) A previous version of this work appeared in a preprint: Buzzetti, L.; Purins, M.; Greenwood, P. D. G.; Waser, J. Enantioselective Carboetherification/Hydrogenation for the Synthesis of Amino Alcohols via a Catalytically-Formed Chiral Auxiliary ChemRxiv, August 25, 2020, ver. 1, DOI: 10.26434/chemrxiv.12855218.v1.