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Dynamic Kinetic Asymmetric [3 + 2] Annulation Reactions of Aminocyclopropanes

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Supporting Information

ABSTRACT: We report the first example of a dynamic kinetic asymmetric [3 + 2] annulation reaction of aminocyclopropanes with both enol ethers and aldehydes. Using a Cu catalyst and a commercially available bisoxazoline ligand, cyclopentyl- and tetrahydrofuryl-amines were obtained in 69−99% yield and up to a 98:2 enantiomeric ratio using the same reaction conditions. The method gives access to important enantio-enriched nitrogen building blocks for the synthesis of bioactive compounds.

The combination of nitrogen functionalities and cyclic structures is omnipresent in bioactive compounds. From the ten most sold pharmaceutical products based on small molecules in 2009, nine contain N-atoms embedded in ring systems.[1] Among the multitude of reported nitrogen-rich cyclic scaffolds, tetrahydrofurylamines and cyclopentylamines occupy a privileged position (Figure 1). Tetrahydrofurylamines are

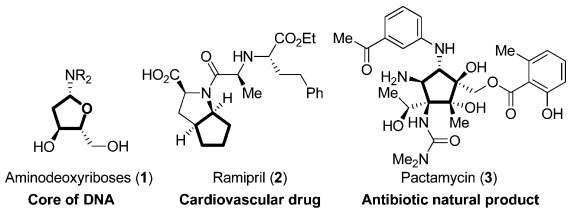
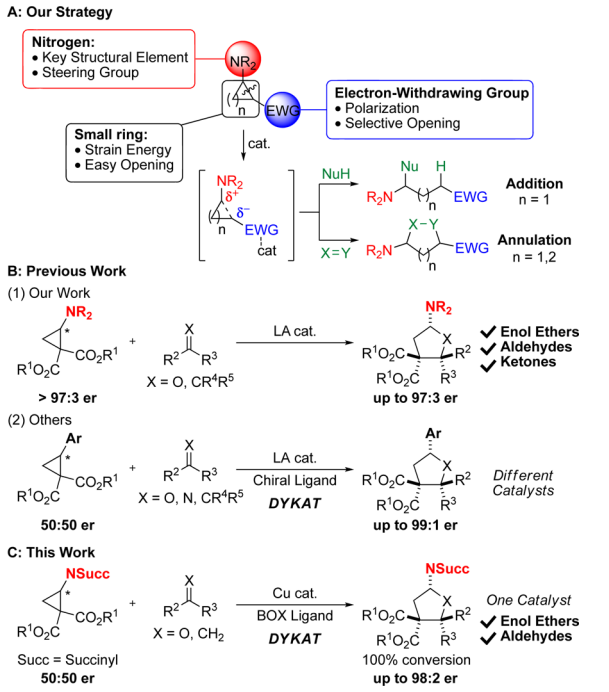


Figure 1. Biomolecules and bioactive compounds containing an amino-tetrahydrofuran or cyclopentane ring.

especially important in the form of aminosugars, such as aminodeoxyriboses **1**, which are at the core of DNA and many bioactive synthetic nucleoside analogues. Cyclopentylamines are well-represented in bioactive compounds, such as the bicyclic drug Ramipril (**2**) used to treat hypertension and heart diseases.[2] They are also at the core of numerous bioactive natural products, such as the antibiotic Pactamycin (**3**).[3] A stereoselective synthetic access to tetrahydrofuryl- and cyclopentylamines would be consequently highly valuable in order to discover new bioactive compounds.

Since 2010, our group has examined the use of donor−acceptor substituted aminocyclopropanes and aminocyclobutanes for the synthesis of nitrogen-rich molecules (Scheme 1A).[4] This approach is particularly attractive, as the N-atom plays a dual role: it is not only an essential structural element of the product but also a steering group to control regioselective ring

Scheme 1. General Strategy (A), Previous Work (B), and Current Work (C) to Access Nitrogen-Rich Building Blocks



opening upon release of ring strain. Despite important progress in the use of donor−acceptor substituted cyclopropanes,[5] only a few examples on the use of aminocyclopropanes had been reported prior to our own work.[6] In our hands, the ring opening of aminocyclopropanes was highly successful for the inter- and intramolecular addition of nucleophiles[4a−c] and the development of new annulation reactions, in particular for the synthesis of cyclopentyl- and tetrahydrofurylamines ((1) in Scheme 1B).[4d−g] The reaction of enol ethers and ketones using a tin catalyst was enantiospecific, whereas the iron-catalyzed annulation of aldehydes gave racemic products.

An approach allowing the complete conversion of easily accessible racemic aminocyclopropanes into enantiopure cyclopentylamines—a dynamic kinetic asymmetric transformation (DYKAT)[7]—would be much more straightforward. Such reactions have been realized for other classes of donor−acceptor cyclopropanes in the past,[8] but have never been reported in the

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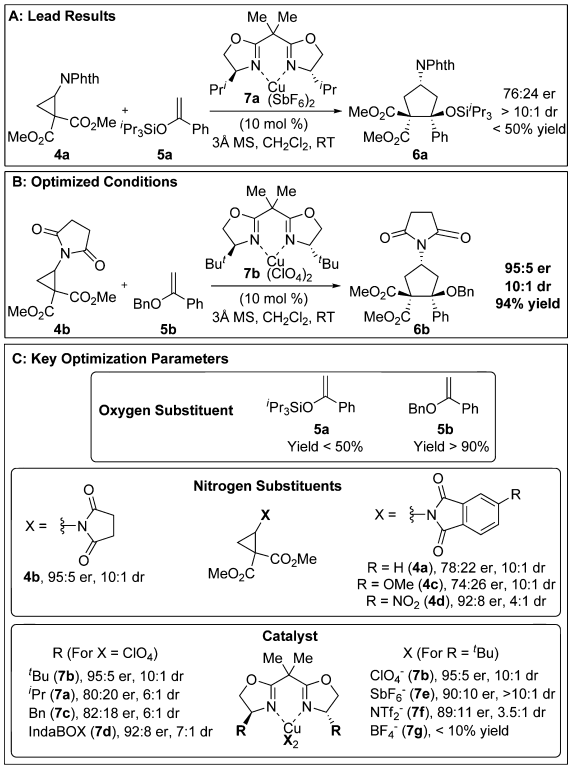
case of aminocyclopropanes ((2) in Scheme 1B). Furthermore, each class of substrates required the development of a unique catalytic system. The synthesis of cyclopentanes has been especially challenging. Success has been limited to the use of cyclic silyl enol ethers[8h] and indoles[8m] as substrates by Tang et al. using a Cu catalyst with specifically designed bisoxazoline ligands.

Herein, we report the first successful dynamic kinetic asymmetric annulation of aminocyclopropanes with enol ethers and aldehydes (Scheme 1C). Enantiomeric ratios up to 98:2 could be achieved with complete conversion of the aminocyclopropane starting material using a simple commercially available bisoxazoline catalyst. In contrast to the only previously reported method for silyl enol ethers,[8h] the transformation was especially successful for noncyclic alkyl enol ethers. The same catalytic system could then be extended to the reaction of aminocyclopropanes with aldehydes to give tetrahydrofurylamines with up to a 96:4 enantiomeric ratio. To the best of our knowledge, this is the first report of an enantioselective catalytic system working for the synthesis of both cyclopentanes and tetrahydrofurans. The obtained enantiopure chiral building blocks will be highly useful for the synthesis of new nitrogen-rich bioactive compounds.

We started our investigations by studying the annulation reaction between phthalimido-substituted dimethyl ester cyclopropane **4a** and silyl enol ether **5a**, as this transformation had already been studied in our previous work involving enantiospecific reactions (Scheme 2).[4d,9] The catalytic system used in this work ($SnCl_4$ at −78 °C) was not well suited for the development of a dynamic kinetic asymmetric transformation, as it was highly enantiospecific at low temperature and led to decomposition at higher temperature. Consequently, a broad range of other catalysts and chiral ligands were examined. From these studies, copper bisoxazoline complex **7a** emerged as the most promising catalyst, leading to complete conversion of cyclopropane **4a** and formation of the cyclopentylamine **6a** in a 76:24 er and a very good diastereoselectivity (Scheme 2A). Nevertheless, the enantioselectivity observed was still not satisfactory and the yield of the isolated product remained low and variable (0−50%) due to the formation of ring-opening side products resulting from a retro-aldol reaction.

Scheme 2. Lead Result (A), Optimized Reaction Conditions (B), and Key Parameters Influencing Yield and Selectivity of the Reaction



To address these shortcomings, extensive optimization of the reaction conditions, cyclopropane and enol ether substituents, and the catalyst structure was performed (Scheme 2B and C).[10] No significant improvement could be obtained by changing the solvent, temperature, concentration, or catalyst loading. In contrast to observations by Tang et al.,[8h] modification of the diester substituents was also not successful. Finally, four parameters were found to be crucial to increase the selectivity and efficiency of the reaction:

(1) Replacing the silyl group on the enol ether by an alkyl group (benzyl) allowed for a significant increase in yield and reproducibility. The higher stability of the carbon−oxygen bond was probably essential to prevent ring-opening side reactions.

(2) The structure of the substituents on the nitrogen was essential to achieve high enantioinduction. The enantiomeric ratio was lower with an electron-donating methoxy substituent on the phthalimide (74:26, cyclopropane **4c**), but increased significantly to 92:8 with a nitro substituent (cyclopropane **4d**). However, this increase of enantioselectivity came at the cost of a lower diastereoselectivity (4:1). Yet, replacing the phthalimide group by a succinimide led to the highest enantiomeric ratio (95:5) without compromising the diastereoselectivity.

(3) Steric hindrance of the substituent on the ligand was another important factor. Best results were obtained with the commercially available bisoxazoline ligand bearing a bulky *tert*-butyl group.

(4) Finally, a strong counteranion effect was observed. The highest enantioinduction was obtained with perchlorate, whereas hexafluoroantimonate led to the highest diastereoselectivity. To obtain high enantioselectivity, it was important to exclude moisture, as the blue copper aqua complex gave lower enantioinduction than the anhydrous green catalyst.

Under the optimized conditions, the desired cyclopentylamine **6b** could finally be obtained in 94% yield and a 95:5 er with good diastereoselectivity (10:1), setting the stage for the investigation of the scope of the reaction (Scheme 1B).

On preparative scale, cyclopentylamine **6b** could be obtained in quantitative yield with a 96:4 er and a 7:1 dr (Table 1, entry 1).Variation of the oxygen substituent was examined first: A methyl enol ether (entry 2) and a more electron-withdrawing trifluoroethyl group (entry 3) both worked in the annulation reaction, but for the latter the diastereoselectivity of the reaction was lost. Variation of the aromatic substituent on the olefin gave comparable enantioinduction for both a *meta* methyl-substituted phenyl ring (entry 4) and a thiophene heterocycle (entry 5). The annulation reaction was not limited to the synthesis of tertiary ethers: unsubstituted benzyl ethers **5g−i** also gave the desired products with useful selectivity (entries 6−8). On a 1 mmol scale, product **6g** was obtained in 80% yield and a 95.5:4.5 er (entry 6).

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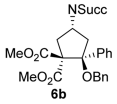
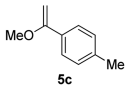
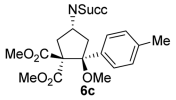
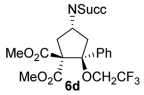
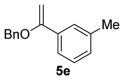
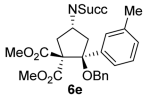
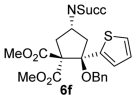
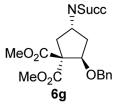
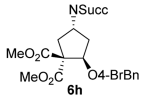
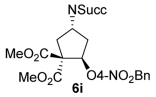
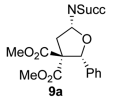
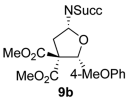
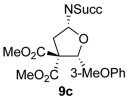
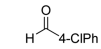
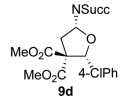
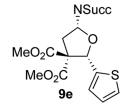
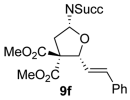
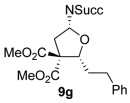
Table 1. Scope of the Annulation Reaction with Enol Ethers[a]

Entry	Enol Ether	Product	Yield[b]/er[c]/dr[d]
1	 **5b**	 **6b**	97% 96:4 er 7:1 dr
2	 **5c**	 **6c**	95% 94.5:5.5 er 20:1 dr
3	 **5d**	 **6d**	88% 95.5:4.5 er[e] 1.5:1 dr
4	 **5e**	 **6e**	99% 95:5 er >20:1 dr
5	 **5f**	 **6f**	94% 94:6 er 8:1 dr
6	 **5g**	 **6g**	96% (80%)[f] 96.5:3.5 (95.5:4.5) er 4:1 (4:1) dr
7	 **5h**	 **6h**	73% 94.5:5.5 er 5:1 dr
8	 **5i**	 **6i**	82% 98:2 er 5:1 dr

[a]Reaction conditions: 0.20 mmol of cyclopropane **4b**, 0.40 mmol of enol ether **5**, 0.02 mmol of catalyst **7b**, 3 Å MS in dichloromethane at rt, under argon. [b]Yield after purification by column chromatography. [c]Determined by chiral phase HPLC. [d]Determined by analysis of crude ^{1}H NMR. [e]Value for major *anti* diastereoisomer, *syn* diastereoisomer: er = 96.5:3.5. [f]Values in brackets correspond to the results on 1 mmol scale.

Table 2. Scope of the Annulation Reaction with Aldehydes[a]

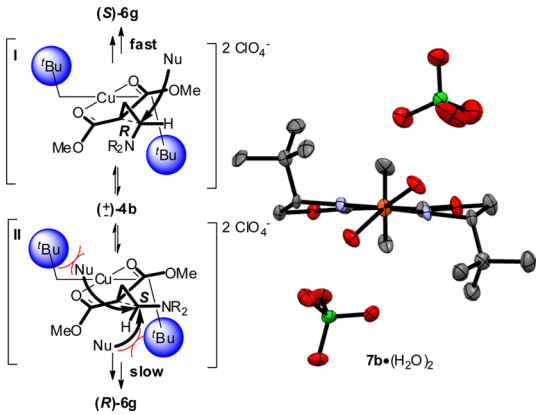
Entry	aldehyde	Product	Yield[b]/er[c]/dr[d]
1	 **8a**	 **9a**	82% 92:8 er 13:1 dr
2	 **8b**	 **9b**	69% 96:4 er >20:1 dr
3	 **8c**	 **9c**	84% 93:7 er 10:1 dr
4	 **8d**	 **9d**	90% 91:9 er 14:1 dr
5	 **8e**	 **9e**	97% 95:5 er >20:1 dr
6	 **8f**	 **9f**	96% 94:6 er 14:1 dr
7	 **8g**	 **9g**	85% 91.5:8.5 er 13:1 dr

[a]Reaction conditions: 0.20 mmol of cyclopropane **4b**, 0.40 mmol of aldehyde **8**, 0.02 mmol of catalyst **7b**, 3 Å MS in dichloromethane at rt, under argon. [b]Yield after purification by column chromatography. [c]Determined by chiral phase HPLC. [d]Determined by analysis of crude ^{1}H NMR.

Achieving high selectivity in DYKAT processes is challenging, and the catalytic system often has to be optimized for each class of substrates. Nevertheless, when benzaldehyde (**8a**) was used in the [3 + 2] annulation process with aminocyclopropane **4b**, the DYKAT process was successful and gave the desired tetrahydrofurylamine **9a** with a 92:8 er and a 13:1 dr (Table 2, entry 1). The annulation reaction was successful for electron-rich (entries 2 and 3) and -poor (entry 4) aromatic aldehydes, as well as for thiophene carboxaldehyde (**8e**) (entry 5). The best enantiomeric ratio (96:4) was observed for the *para*-methoxy substituted benzene ring (entry 2). The reaction was not limited to aromatic aldehydes: both cinnamaldehyde (**8f**) (entry 6) and aliphatic aldehyde **8g** (entry 7) could be used.

The absolute configuration of **6g** was determined by X-ray crystallography (*S* at the center next to the N-atom).[11,12] Interestingly, the absolute configuration is opposite to the one obtained by Tang et al.[8h,m] Although further experiments will be required to establish the origin of asymmetric induction, we propose a tentative stereochemical model based on the strong distortion from the square planar geometry in *tert*-butyl-substituted bisoxazoline complexes, which is also apparent in the *bis*-aqua complex of **7b** (Scheme 3).[13] In complex **I**, formed

Scheme 3. Stereochemical Model for the Reaction and X-ray Structure of Complex 7b·$(H_2O)_2$[14]



from the *R* enantiomer of cyclopropane **4b**, the distortion moves the cyclopropane to the upper right quadrant, opening a free path for fast attack of the nucleophile and affording the product with the observed absolute configuration. In complex **II** formed from the *S* enantiomer, the attack of the nucleophile is blocked by the *tert*-butyl substituents of the ligand and is, therefore, slower. The dynamic process can be speculated to proceed via reversible ring opening/closing, as racemization of enantio-enriched **4b** was observed in the absence of the enol ether.[15]

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In summary, we have reported the first example of a dynamic kinetic asymmetric [3 + 2] annulation reaction of aminocyclopropanes. The reaction proceeded with high enantio- and diastereoselectivity with a broad range of acyclic alkyl enol ethers and aldehydes using a Cu catalyst with a commercially available bisoxazoline ligand. Importantly, the developed catalytic system could be used for both types of substrates without reoptimization. The method is expected to be highly useful for the asymmetric synthesis of nitrogen-rich small organic molecules.

■ 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.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348.

(2) Yusuf, S.; Teo, K. K.; Pogue, J.; Dyal, L.; Copland, I.; Schumacher, H.; Ingelheim, B.; Dagenais, G.; Sleight, P.; Anderson, C. *N. Engl. J. Med.* **2008**, *358*, 1547.

(3) (a) Brodersen, D. E.; Clemons, W. M.; Carter, A. P.; Morgan-Warren, R. J.; Wimberly, B. T.; Ramakrishnan, V. *Cell* **2000**, *103*, 1143. (b) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180.

(4) Additions: (a) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767. (b) de Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* **2013**, *15*, 3738. (c) Frei, R.; Staedler, D.; Raja, A.; Franke, R.; Sasse, F.; Gerber-Lemaire, S.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13373. Annulations: (d) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. (e) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem.—Eur. J.* **2012**, *18*, 4844. (f) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386. (g) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9009.

(5) (a) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (d) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353. (e) Lebold, T. P.; Kerr, M. A. *Pure Appl. Chem.* **2010**, *82*, 1797. (f) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293. (g) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848. (h) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969.

(6) For selected examples, see: (a) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (b) Ha, J. D.; Lee, J. W.; Blackstock, S. C.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 8510. (c) Williams, C. M.; de Meijere, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3699. (d) Larquetoux, L.; Ouhamou, N.; Chiaroni, A.; Six, Y. *Eur. J. Org. Chem.* **2005**, 4654. (e) Madelaine, C.; Six, Y.; Buriez, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 8046. (f) Yang, J.; Wu, H. X.; Shen, L. Q.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794. (g) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447. For recent examples reported after publication of our work, see: (h) Gharpure, S. J.; Vijayasree, U.; Reddy, S. R. B. *Org. Biomol. Chem.* **2012**, *10*, 1735. (i) Maity, S.; Zhu, M. Z.; Shinabery, R. S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 222. (j) Rivero, A. R.; Fernandez, I.; Sierra, M. A. *Org. Lett.* **2013**, *15*, 4928. (k) Tejero, R.; Ponce, A.; Adrio, J.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 10406. This last reference contains a single example of aminocyclopropane.

(7) Steinreiber, J.; Faber, K.; Griengl, H. *Chem.—Eur. J.* **2008**, *14*, 8060.

(8) DYKAT: (a) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122. (b) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688. (c) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558. (d) Trost, B. M.; Morris, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6167. (e) Trost, B. M.; Morris, P. J.; Sprague, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 17823. (f) Mei, L. Y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2012**, *31*, 7591. (g) Mei, L. Y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2013**, *32*, 3544. (h) Xu, H.; Qu, J. P.; Liao, S. H.; Xiong, H.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4004. Only the examples based on cyclopropanes as limiting substrates are listed. Kinetic resolutions and other asymmetric transformations: (i) Sibi, M. P.; Ma, Z. H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (j) Kang, Y. B.; Sun, X. L.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3918. (k) Zhou, Y. Y.; Wang, L. J.; Li, J.; Sun, X. L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066. (l) Zhou, Y. Y.; Li, J.; Ling, L.; Liao, S. H.; Sun, X. L.; Li, Y. X.; Wang, L. J.; Tang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1452. (m) Xiong, H.; Xu, H.; Liao, S. H.; Xie, Z. W.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851. (n) Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618.

(9) The enol ethers and cyclopropanes used in this study were synthesized using modified reported procedures: Enol ethers: (a) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225. Cyclopropanes: (b) Bayer, E.; Geckeler, K. *Angew. Chem., Int. Ed.* **1979**, *18*, 533. (c) Baret, N.; Dulcere, J. P.; Rodriguez, J.; Pons, J. M.; Faure, R. *Eur. J. Org. Chem.* **2000**, 1507. (d) Kacprzak, K. *Synth. Commun.* **2003**, *33*, 1499. (e) Wyatt, P.; Hudson, A.; Charmant, J.; Orpen, A. G.; Phetmung, H. *Org. Biomol. Chem.* **2006**, *4*, 2218. (f) Gonzalez-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal.* **2008**, *350*, 813. See Supporting Information (SI) for detailed procedures.

(10) For easier comparison, the values given in Scheme 2C have been limited to those obtained when changing a single parameter from the optimized conditions given in Scheme 2B. For the optimization studies, the yields and diastereoselectivities were calculated by NMR and the er was determined by chiral HPLC; see SI for further details.

(11) See Figure S1 in the Supporting Information.

(12) As in the proposed model, the absolute configuration is determined only by the trajectory of attack of the nucleophile on the cyclopropane; the same absolute configuration is proposed for the tetrahydrofuran products. Further investigations will be needed to confirm the configuration and study the mechanism of formation of the tetrahydrofuran products.

(13) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (b) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2011**, *111*, PR284. See also Figure S2 in the SI for a simplified stereochemical model with different complex geometries.

(14) The hydrogen atoms are omitted for clarity.

(15) Cyclopropane **4b** was obtained with a 59:41 er via cyclopropanation with a chiral rhodium catalyst. Complete racemization was observed after 30 min in presence of catalyst **7b**. Addition of the nucleophile to the diastereomeric complexes is proposed (DYKAT type I), but reaction of the Cu bond iminium intermediate could also be considered (DYKAT type II). See SI for further details.