Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2014, **5**, 1928

Enantioenriched β-lactone and aldol-type products from regiodivergent carbonylation of *racemic cis*-epoxides†

Michael Mulzer, W. Chadwick Ellis, Emil B. Lobkovsky and Geoffrey W. Coates*

Received 8th January 2014
Accepted 19th February 2014

DOI: 10.1039/c4sc00075g

www.rsc.org/chemicalscience

A new carbonylation catalyst is reported that provides enantioenriched β-lactones and aldol-type products from the carbonylative ring-expansion of *racemic cis*-epoxides. Detailed analysis of the reaction demonstrates that the epoxide substrates undergo regiodivergent carbonylation reactions instead of traditional kinetic resolutions. This new catalytic system was applied to the synthesis of a key fragment of the antibiotic Globomycin.

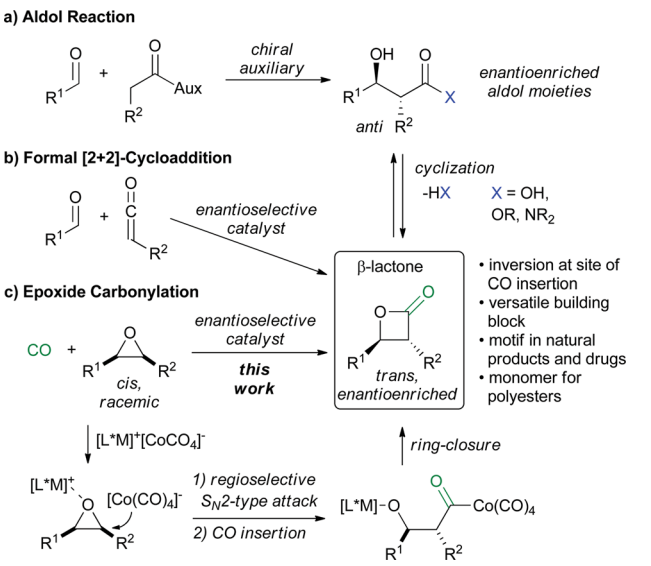
Introduction

β-Lactones have a long-standing history as valuable and versatile compounds in chemical synthesis. Examples of their application include the synthesis of natural products,[1] pharmaceutical compounds,[2] (biodegradable) polyesters,[3] value-added products with structural complexity,[4] as well as the labeling of proteins.[5] Moreover, the high intrinsic reactivity of the strained β-lactone ring allows reaction with a variety of nucleophiles to form products typically associated with aldol chemistry (Scheme 1).[6,7] Aldol moieties are also important motifs in natural products.[8]

Although a variety of synthetic methodologies exist to access β-lactone products, methods for the direct, economical and enantioselective synthesis of β-lactones are still limited,[9] thus restricting their utility. In the past, aldol chemistry has often been used to access enantioenriched β-lactones (Scheme 1a).[6] Many highly diastereo- and enantioselective aldol reactions are available to furnish suitable intermediates[10] that can then be cyclized to the desired β-lactone.[6] However, most aldol methodologies suffer from the requirements of preformed enolate-equivalents together with enantiopure auxiliaries or catalysts. As a result, this route can be impractical, although recent developments in the field of asymmetric direct aldol reactions may alleviate these limitations.[11]

A more recent approach yielding enantioenriched β-lactones directly is based on (formal) [2 + 2]-cycloadditions of aldehydes with ketenes (Scheme 1b).[12] While this route routinely gives *cis*-β-lactones with high stereoselectivity, only a few catalytic systems for the synthesis of enantioenriched *trans*-β-lactones have been reported.[13,14] Moreover, these methods generally require relatively high catalyst loadings, low reaction temperatures, and sometimes stoichiometric amounts of additional reagents.

Another direct approach to β-lactones is the carbonylation of epoxides using catalysts of the form [Lewis acid]$^+$ [Co(CO)$_4$]$^-$ (Scheme 1c).[15] This method is attractive because carbon monoxide and diastereopure epoxides are readily available. In addition, the transformation is proposed to proceed by an S_N2-mechanism,[16] which reliably converts, for example, *cis*-epoxides into *trans*-β-lactones. However, enantioselective variants of these reactions[16a,17] still have not reached synthetic maturity, and have been declared a major challenge for the field.[18]



Scheme 1 Approaches to enantioenriched *anti*-aldol adducts and *trans*-β-lactones.

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York, 14853, USA. E-mail: coates@cornell.edu

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of all new compounds, crystallographic data for (*R*)-**1b**, further data in support of Table 3, Fig. 2, and Fig. 3. CCDC 980420. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4sc00075g

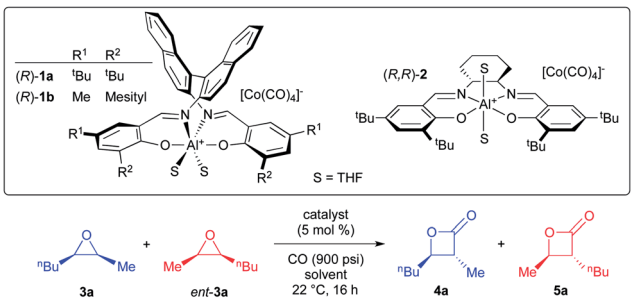
In an effort to advance the field of asymmetric epoxide carbonylation, we herein report a new enantiopure catalyst which is active for the regiodivergent carbonylation of *racemic cis*-disubstituted epoxides. The resulting β-lactones showed good to high enantiomeric excess and *trans*-configuration, which complements advances in the field of [2 + 2]-cycloadditions. Furthermore, the β-lactones were easily converted into enantioenriched *anti*-aldol-type products. The fact that such aldol-products are less readily available than their *syn*-counterparts by either aldol reactions[19,20] or [2 + 2]-cycloadditions further underscores the importance of our study.

Results and discussion

As part of ongoing studies concerning the development of salen-based catalysts for the regioselective carbonylation of *cis*-disubstituted epoxides,[21] we became interested in atropisomeric 2,2′-diamino-1,1′-binaphthalene (DABN) as a chiral structural unit in the ligand framework.[22] Screening reactions using an enantiopure DABN-based catalyst such as (*R*)-**1a** (Table 1) revealed that appreciable amounts of enantioenrichment can be induced in the resulting lactones despite full conversion of the *racemic* epoxide (entry 1). A kinetic resolution could not account for this observation, whereas invoking the occurrence of a regiodivergent reaction[23] could. Interestingly, regiodivergent reactions based on S_N2-mechanisms are rare, especially with epoxides as substrates.[24]

The outcome of this reaction was further improved using catalyst (*R*)-**1b**, which features salicylaldehyde-units bearing sterically hindered mesityl-groups as substituent R^2 (entry 2).

Table 1 Evaluation of enantiopure [Lewis acid]$^+$ [Co(CO)$_4$]$^-$ catalysts and solvents for the regiodivergent carbonylation of *cis*-epoxides



Entry	Catalyst	Solvent	Conv.[a] (%)	Ratio **4a** : **5a**[a]	%ee of **4a**[a]	%ee of **5a**[a]
1	(*R*)-**1a**	THF	94	65 : 35	30	49
2	(*R*)-**1b**	THF	96	45 : 55	94	83
3	(*R*)-**1b**	Toluene	98	45 : 55	86	73
4	(*R*)-**1b**	Et_2O	99	46 : 54	87	77
5	(*R*)-**1b**	DME	28	39 : 61	58	79
6	(*R*)-**1b**	THP	97	44 : 56	87	72
7	(*R*)-**1b**	Dioxane	99	44 : 56	85	72
8	(*R*,*R*)-**2**	THF	98	73 : 27	<1	8

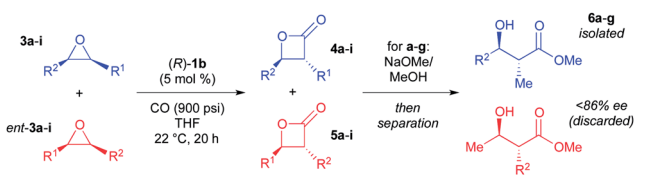
[a] Conversion to respective β-lactone and enantiomeric excess determined by GC analysis. Catalysts (*R*)-**1a,b** were generated *in situ* (L_nAlCl + $NaCo(CO)_4$). Mesityl = 2,4,6-Me_3-phenyl.

This complex was designed using the hypothesis that the larger rigid aromatic groups might carve out a more enantioselective cleft for epoxide binding. Use of this catalyst gave complete conversion of *rac*-**3a** and yielded highly/moderately enantioenriched lactones **4a** and **5a**, respectively. Given the good results with (*R*)-**1b**, further attempts were made to increase the enantiomeric excess of **5a** by using different solvents. However, none of the solvents tested surpassed the results obtained with THF (entries 3–7). As expected, previously reported catalysts such as (*R*,*R*)-**2**[16a] failed to reach similar levels of selectivity (entry 8).

Encouraged by the performance of (*R*)-**1b**, the scope of this reaction using a variety of *racemic cis*-disubstituted epoxides (**3a–i**) was investigated (Table 2). The resulting lactones (**4a–i** and **5a–i**) all showed good to high levels of enantioenrichment, but none of them could be separated quantitatively using flash column chromatography. However, more advanced separation techniques such as preparative HPLC or GC chromatography should be able to address this problem. In addition, this inseparability is of little concern if one is interested in the resulting aldol-type products, because ring-opening of lactones **4a–g** and **5a–g** to the corresponding methyl-esters, for example, enabled facile separation of the two species. Using this approach, lactones **4a–g** were converted into methyl-esters **6a–g** *via* a one-pot procedure, and isolated as such. Lactones **5a–g** (with R^1 = Me) generally showed less than 86% ee, which did not warrant isolation of their ester-derivatives.

Good yields and enantioselectivities of 93% ee or better were achieved for methyl-esters **6a–e** bearing linear alkyl-chains of varying length as R^2 (entries 1–5). Epoxides with branching in R^2 performed equally well and produced esters **6f–g** with comparable yields and enantioenrichment (entries 6 and 7).

Table 2 Scope of the regiodivergent carbonylation of *racemic cis*-epoxides **3** using (*R*)-**1b**[a]



Entry	R^1	R^2	Product isolated	Isolated yield (%)	%ee[b]
1	Me	Et	**6b**	38	94
2	Me	^{n}Pr	**6c**	32	93
3	Me	^{n}Bu	**6a**	36	94
4	Me	^{n}Pent	**6d**	36	94
5	Me	^{n}Hex	**6e**	33	95
6	Me	$(CH_2)_2{}^i$Pr	**6f**	36	94
7	Me	$(CH_2)_3$OTBS	**6g**	35	92
8	Et	^{n}Pr	**4h** + **5h** (44 : 56)[c]	61[d]	96 (**4h**), 93 (**5h**)
9	Et	^{n}Bu	**4i** + **5i** (44 : 56)[c]	73[d]	96 (**4i**), 90 (**5i**)

[a] All reactions gave full conversion by GC analysis. [b] Enantiomeric excess determined by GC analysis. [c] Product ratio of **4** to **5** as determined by GC analysis. [d] Isolated yield of combined β-lactones **4** and **5**. TBS = ^{t}BuMe$_2$Si. Catalyst (*R*)-**1b** was generated *in situ* (L_nAlCl + $NaCo(CO)_4$). For a more detailed Table 2, see ESI.

Ethyl-substituted epoxides **3h** and **i** also gave good enantiomeric excess for **4** and **5** (entries 8 and 9), but as expected their ester-derivatives were difficult to separate. Therefore, a mixture of the two lactones was isolated in both cases. Overall, (*R*)-**1b** proved to be a suitable catalyst for the production of enantioenriched lactones **4** and the corresponding esters **6** from *racemic cis*-epoxides **3**.

Despite the good results that (*R*)-**1b** achieved, some limitations with regard to scope remain. For example, it seems pivotal that one of the epoxide substituents is a methyl- or ethyl-group, and that steric bulk is not situated too close to the epoxy-group. In addition, the catalyst presently does not tolerate epoxides bearing protic, Brønsted-acidic or Lewis-basic functional groups. *trans*-Epoxides also did not furnish good results when using (*R*)-**1b** under standard reaction conditions.[25]

Another weakness of (*R*)-**1b** is that it furnishes only one of the two lactones in highly enantioenriched form at the conclusion of the carbonylation reaction. This outcome automatically restricts the potential utility of this transformation to <50% yield. In an attempt to ameliorate this limitation, we modified catalyst (*R*)-**1b** further, so that it is capable of providing both resulting lactones in high ee (Scheme 2). A more detailed account regarding this catalytic system (*R*)-**1c** will be reported elsewhere.[26]

Single crystals of (*R*)-**1b** were obtained and subjected to X-ray analysis to further understand the structure of this catalyst (Fig. 1). The solid state structure shows the expected ion pair composed of chiral aluminum cation and the tetracarbonylcobaltate anion. Interestingly, the ligand around the aluminum-ion adopts a *cis*-α geometry, which is a departure from the *trans*-planar structures of previously reported salen-based carbonylation catalysts.[15] The strong twist imposed by the DABN-unit in combination with the steric interaction of the mesityl-groups are most likely the main causes for this arrangement of the ligand. In support of this, an analog of (*R*)-**1a** shows a *cis*-β geometry,[27] whereas use of a more flexible diamine-unit gives a *trans*-planar coordinated salen-complex.[28] Nonetheless, this geometry allows for formation of a rigid and C_2-symmetric chiral pocket occupied by two THF-molecules. This structure also explains why DME was a particularly poor solvent for (*R*)-**1b** (Table 1, entry 5). DME can act as a bidentate ligand, thus occupying both *cis*-coordination sites. Due to the chelate effect, it outcompetes with epoxide molecules for binding to the aluminum center.

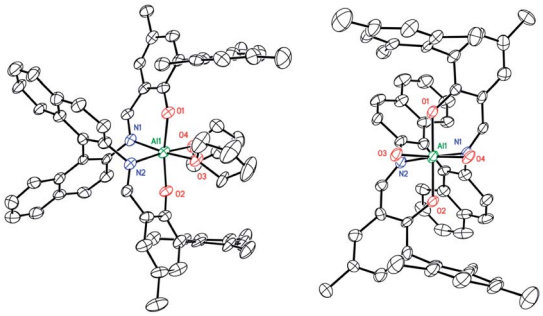


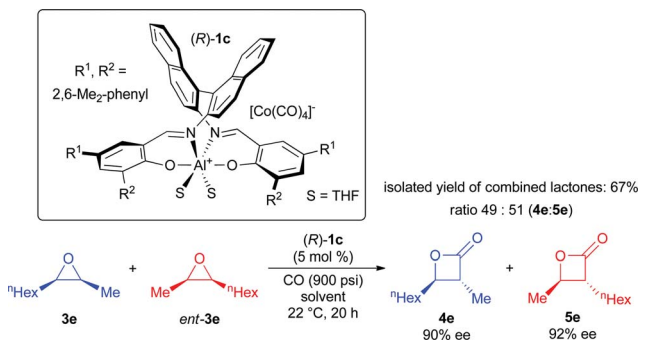
Fig. 1 ORTEP-representations of (*R*)-**1b** (50% probability thermal ellipsoids). Hydrogen atoms and cobaltate-counterion are omitted for clarity, as are the THF ligands in the structure to the right.

Having established the scope of this transformation for a variety of *racemic cis*-epoxides, the course of the reaction and factors responsible for its outcome were subsequently investigated. As mentioned before, a regiodivergent reaction explains the results obtained. A prerequisite for such a reaction would be that (*R*)-**1b** carbonylates both enantiomers of a given epoxide **3** with high and opposing regioselectivities. To confirm this hypothesis, an enantiopure sample of **3a** (99% ee) was carbonylated with both enantiomers of catalyst **1b** (Scheme 3).

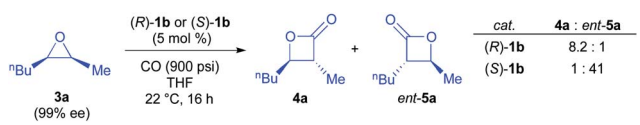
As Scheme 3 shows, carbonylation of enantioenriched **3a** occurred with high and opposing regioselectivities when using (*R*)- and (*S*)-**1b**. Interestingly, the two enantiomers of **1b** showed some degree of a matched/mismatched pair with **3a**. (*R*)-**1b** carbonylated **3a** only with a regioselectivity of 8.2 : 1 with regard to **4a** and *ent*-**5a**. Contrary to that, (*S*)-**1b** gave a much better ratio of 1 : 41 in favor of *ent*-**5a**. The same result, namely a ratio of 1 : 41 favoring **5a**, should obviously be obtained if (*R*)-**1b** were to react with enantiopure *ent*-**3a**. Consequently, enantiopure **1b** fulfills the requirement necessary for a regiodivergent reaction, namely providing high and opposing regioselectivities.

The results from Scheme 3 also allow for two more conclusions. First, (*R*)-**1b** can be used to regioselectively carbonylate enantiopure *cis*-epoxides **3**. Secondly, the data in Scheme 3 allows for calculation of the theoretically expected enantiomeric ratios for **4a** and **5a** in the regiodivergent carbonylation of *rac*-**3a** using (*R*)-**1b**.[29] Generally, good agreement between theoretically predicted values and experimental data was observed (Table 3).

In a separate set of experiments, the carbonylation of *rac*-**3a** with (*R*)-**1b** was monitored in detail using chiral GC analysis.[29]

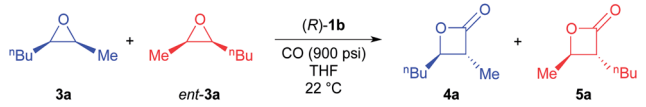


Scheme 2 Preliminary result concerning the regiodivergent carbonylation of epoxides **3** using catalyst (*R*)-**1c**. Reaction gave full conversion by GC analysis. Enantiomeric excess determined by GC analysis, and product ratio determined by ^{1}H NMR analysis.



Scheme 3 Regioselectivity in the carbonylation of enantiopure **3a** using (*R*)- and (*S*)-**1b**. The ratio **4a** : *ent*-**5a** was determined *via* ^{1}H NMR analysis of crude reaction mixture (conv. >95% by GC analysis). Catalysts (*R*)- and (*S*)-**1b** were generated *in situ* (L_nAlCl + $NaCo(CO)_4$).

Table 3 Regiodivergent carbonylation of *racemic* **3a** using (*R*)-**1b**: predicted and experimentally observed values for enantiomeric ratio (er) and ratio of regioisomers[a]



Entry	Property	Value
1	Theoretical ratio **4a** : **5a**	45.8 : 54.2
2	Experimentally observed ratio **4a** : **5a**	44.9 : 55.1
3	Theoretical er of **4a**	97.4 : 2.6
4	Experimentally observed er of **4a**	97.3 : 2.7
5	Theoretical er of **5a**	90.0 : 10.0
6	Experimentally observed er of **5a**	91.1 : 8.9

[a] Experimental values were determined from crude reaction mixture by ^{1}H NMR analysis (for product ratio) and GC analysis (for enantiomeric ratios). Predicted values were calculated as shown in the ESI. er = enantiomeric ratio. Full conversion of the epoxide was assumed in both cases.

The resulting data (Fig. 2) showed that (*R*)-**1b** consumed both enantiomers of the epoxide with comparable activity, with *ent*-**3a** reacting faster than **3a** by a factor of approximately four (*vide infra*). This observation rules out a transient kinetic resolution of the epoxide. Trace amounts of ketone side products, which stem from isomerization of the epoxide,[15d] were also detected, and steadily increased as the reaction progressed.[29] Moreover, the collected data indicated that **5a**, the β-lactone preferentially formed by (*R*)-**1b** from *ent*-**3a** (*cf.* Scheme 3 and Fig. 4), is the lactone that is formed fastest and initially in >90% ee. Lactone **4a**, on the other hand, is produced slower and at first only with <80% ee. However, as the reaction progressed more of the other epoxide enantiomer **3a** was consumed, which causes the enantiomeric ratio of **5a** to slowly deteriorate. As shown in Fig. 4, this is due to the fact that **3a** gives rise to **4a** and small amounts of *ent*-**5a**. Consequently, the %ee of **4a** steadily improves as that of **5a** declines, until **4a** reaches the excellent % ee that is observed upon completion of the reaction.

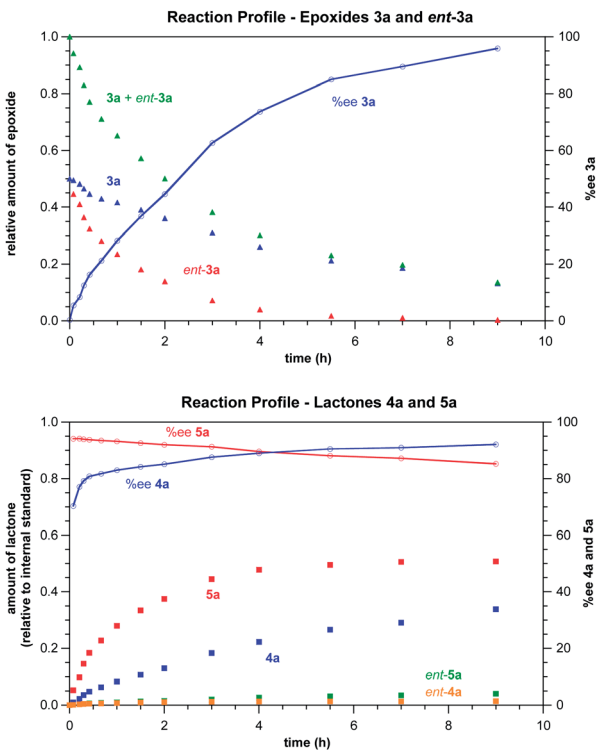


Fig. 2 Reaction profiles of major species present in the regiodivergent carbonylation of *rac*-**3a** using (*R*)-**1b**.

Monitoring the reaction of *rac*-**3a** with (*R*)-**1b** also allowed for an approximation of the selectivity factor (*s*) with regard to the epoxide. These data can be estimated by plotting conversion of epoxide against its enantiomeric excess over the course of the reaction.[29] The distribution of the data points in the resulting plot varies in a characteristic way depending on the selectivity factor (*s*) and the reaction order in substrate in the selectivity-determining step. In the case of *rac*-**3a**, the resulting plot (Fig. 3) resembled graphs that are associated with a first order dependence in substrate.[29] This is an interesting observation because previous studies[16b] showed that salen-based carbonylation catalysts convert terminal epoxides with a zero order dependence in substrate in the rate law.

Moreover, a simulated curve representing a first order dependence and a selectivity factor (*s*) of *ca.* 4 adequately reproduced the experimental data points (black line in Fig. 3), and thus should provide a good estimate for the selectivity factor (*s*) displayed by (*R*)-**1b** with *rac*-**3a**. Finally, Fig. 4 summarizes the relevant data discussed regarding the detailed analysis of the regiodivergent carbonylation of *rac*-**3a** using (*R*)-**1b**.

Lastly, to demonstrate the applicability of the regiodivergent carbonylation methodology (*R*)-**1b** was used to synthesize Fragment A (7) of Globomycin[30] starting from *racemic* epoxide **3e** (Scheme 4). Globomycin is a promising antibiotic against Gram-negative bacteria and can also act as a specific inhibitor of certain signal peptidases. Furthermore, the activity of Globomycin depends strongly on the actual length of the alkyl chain in Fragment A.[30b,c]

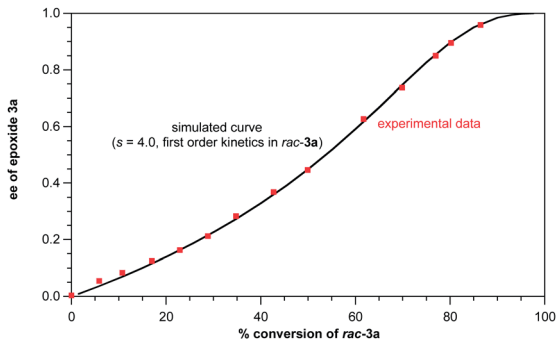


Fig. 3 Plot of conversion *versus* enantiomeric excess of epoxide **3a** in the regiodivergent carbonylation of *rac*-**3a** using (*R*)-**1b**. The black line represents a simulated curve based on a first order consumption of the epoxide in the selectivity-determining step, and corresponds to a selectivity factor (*s*) of 4.0.

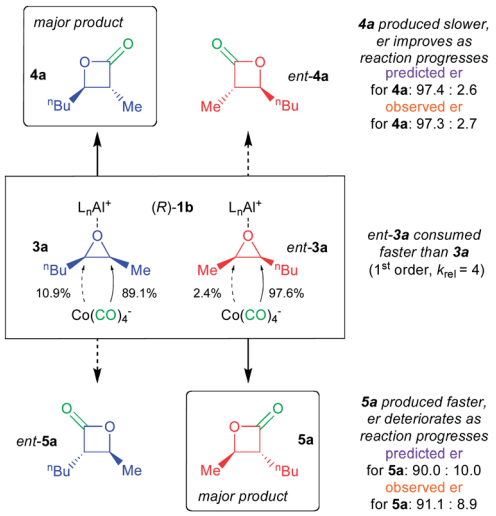
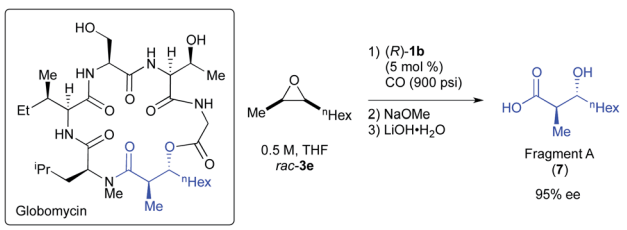


Fig. 4 Stereochemical analysis of the carbonylation of *rac*-**3a** by (*R*)-**1b** (reaction conditions: 900 psi CO, THF, 22 °C).



Scheme 4 Synthesis of Fragment A (**7**) of Globomycin using regiodivergent carbonylation.

Fragment **7** was obtained in an unoptimized 30% yield (60% of maximum theoretical yield) starting from *rac*-**3e**, and its exclusive *anti*-stereochemistry and 95% ee compares favorably to the 92% ee reported in the literature for this compound using an aldol approach.[30a] Even more important is that regiodivergent carbonylation is well suited to deliver derivatives of **7** for structure–reactivity relationship studies with comparable enantioselectivities as seen in Table 2.

Conclusions

In conclusion, a new enantiopure carbonylation catalyst (*R*)-**1b** was reported and applied to the regiodivergent carbonylation of *racemic cis*-disubstituted epoxides. The products were enantioenriched *trans*-β-lactones showing 90% ee or better, which were further elaborated into *anti*-aldol products in a one-pot sequence. The effectiveness of (*R*)-**1b** in inducing enantioenrichment was attributed to the *cis*-α coordination geometry of the ligand around the Lewis acidic metal-ion. Moreover, the reaction of *racemic* epoxide **3a** with (*R*)-**1b** was studied in detail to confirm that **3a** underwent a regiodivergent carbonylation reaction. Lastly, regiodivergent carbonylation was applied to the synthesis of an important fragment of Globomycin. Future work will focus on the further development of enantioselective carbonylation catalysts as well as new reactions involving catalysts bearing enantiopure ligands of type **1b**.

Acknowledgements

This work was supported by the Department of Energy (DE-FG02-05ER15687).

Notes and references

1 A. Pommier and J.-M. Pons, *Synthesis*, 1995, 729.
2 For example see: P.-Y. Yang, K. Liu, M. Hong Ngai, M. J. Lear, M. R. Wenk and S. Q. Yao, *J. Am. Chem. Soc.*, 2010, **132**, 656.
3 (*a*) H.-M. Müller and D. Seebach, *Angew. Chem., Int. Ed.*, 1993, **32**, 477; (*b*) M. Okada, *Prog. Polym. Sci.*, 2002, **27**, 87.
4 W. Ren, Y. Bian, Z. Zhang, H. Shang, P. Zhang, Y. Chen, Z. Yang, T. Luo and Y. Tang, *Angew. Chem., Int. Ed.*, 2012, **51**, 6984.
5 J. W. Amoroso, L. S. Borketey, G. Prasad and N. A. Schnarr, *Org. Lett.*, 2010, **12**, 2330.
6 For reviews see: (*a*) A. Pommier and J.-M. Pons, *Synthesis*, 1993, 441; (*b*) Y. Wang, R. L. Tennyson and D. Romo, *Heterocycles*, 2004, **64**, 605.
7 For recent examples see: (*a*) S. G. Nelson and K. L. Spencer, *Angew. Chem., Int. Ed.*, 2000, **39**, 1323; (*b*) S. G. Nelson and Z. Wan, *Org. Lett.*, 2000, **2**, 1883; (*c*) S. G. Nelson, Z. Wan and M. A. Stan, *J. Org. Chem.*, 2002, **67**, 4680; (*d*) M. Mondal, A. A. Ibrahim, K. A. Wheeler and N. J. Kerrigan, *Org. Lett.*, 2010, **12**, 1664.
8 (*a*) B. Schetter and R. Mahrwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7506; (*b*) T. Brodmann, M. Lorenz, R. Schäckel, S. Simsek and M. Kalesse, *Synlett*, 2009, 174; (*c*) J. Li and D. Menche, *Synthesis*, 2009, **14**, 2293.
9 For reviews see: (*a*) H. W. Yang and D. Romo, *Tetrahedron*, 1999, **55**, 6403; (*b*) R. K. Orr and M. A. Calter, *Tetrahedron*, 2003, **59**, 3545.
10 For reviews see: (*a*) R. Mahrwald, *Chem. Rev.*, 1999, **99**, 1095; (*b*) C. Palomo, M. Oiarbide and J. M. García, *Chem. Soc. Rev.*, 2004, **33**, 65; (*c*) R. Mahrwald, *Aldol Reactions*, Springer, London, 2009; (*d*) G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076.
11 For reviews see: (*a*) G. Guillena, C. Nájera and D. J. Ramón, *Tetrahedron: Asymmetry*, 2007, **18**, 2249; (*b*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*c*) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600.
12 For recent examples see: (*a*) J. E. Wilson and G. C. Fu, *Angew. Chem., Int. Ed.*, 2004, **43**, 6358; (*b*) S. G. Nelson, C. Zhu and X. Shen, *J. Am. Chem. Soc.*, 2004, **126**, 14; (*c*) C. Zhu, X. Shen and S. G. Nelson, *J. Am. Chem. Soc.*, 2004, **126**, 5352; (*d*) S. H. Oh, G. S. Cortez and D. Romo, *J.Org. Chem.*, 2005, **70**, 2835; (*e*) V. C. Purohit, R. D. Richardson, J. W. Smith and D. Romo, *J. Org. Chem.*, 2006, **71**, 4549.
13 (*a*) M. A. Calter, O. A. Tretyak and C. Flaschenriem, *Org. Lett.*, 2005, **7**, 1809; (*b*) T. Kull and R. Peters, *Angew. Chem., Int. Ed.*,

2008, **47**, 5461; (*c*) T. Kull, J. Cabrera and R. Peters, *Chem.–Eur. J.*, 2010, **16**, 9132; (*d*) P. Meier, F. Broghammer, K. Latendorf, G. Rauhut and R. Peters, *Molecules*, 2012, **17**, 7121; (*e*) ref. 7*d*.

14 The synthesis of *trans*-β-lactones *via* epimerization of *cis*-β-lactones or α-alkylation of β-monosubstituted β-lactones is not trivial. For example see: (*a*) A. Griesbeck and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1320; (*b*) ref. 12*e*.

15 (*a*) Y. D. Y. L. Getzler, V. Mahadevan, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2002, **124**, 1174; (*b*) V. Mahadevan, Y. D. Y. L. Getzler and G. W. Coates, *Angew. Chem., Int. Ed.*, 2002, **41**, 2781; (*c*) J. A. R. Schmidt, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2005, **127**, 11426; (*d*) J. W. Kramer, E. B. Lobkovsky and G. W. Coates, *Org. Lett.*, 2006, **8**, 3709; (*e*) T. L. Church, Y. D. Y. L. Getzler, C. M. Byrne and G. W. Coates, *Chem. Commun.*, 2007, 657; (*f*) Q. Chen, M. Mulzer, P. Shi, P. J. Beuning, G. W. Coates and G. A. O'Doherty, *Org. Lett.*, 2011, **13**, 6592.

16 (*a*) Y. D. Y. L. Getzler, V. Mahadevan, E. B. Lobkovsky and G. W. Coates, *Pure Appl. Chem.*, 2004, **76**, 557; (*b*) T. L. Church, Y. D. Y. L. Getzler and G. W. Coates, *J. Am. Chem. Soc.*, 2006, **128**, 10125.

17 (*a*) H. Wölfle, H. Kopacka, K. Wurst, P. Preishuber-Pflügl and B. Bildstein, *J. Organomet. Chem.*, 2009, **694**, 2493; (*b*) P. Ganji and H. Ibrahim, *Chem. Commun.*, 2012, **48**, 10138.

18 K. Naka and K. Nozaki, *Top. Organomet. Chem.*, 2006, **18**, 223.

19 For recent examples see: (*a*) D. A. Evans, J. S. Tedrow, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2002, **124**, 392; (*b*) Y. Yamashita, H. Ishitani, H. Shimizu and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 3292; (*c*) S. E. Denmark, T. Wynn and G. L. Beutner, *J. Am. Chem. Soc.*, 2002, **124**, 13405; (*d*) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798; (*e*) A. K. Ghosh and J.-H. Kim, *Org. Lett.*, 2003, **5**, 1063; (*f*) M. T. Crimmins and P. J. McDougall, *Org. Lett.*, 2003, **5**, 591; (*g*) H. Nishiyama, T. Shiomi, Y. Tsuchiya and I. Matsuda, *J. Am. Chem. Soc.*, 2005, **127**, 6972.

20 Organocatalysis has enabled some very enantio- and diastereoselective aldol reactions. However, *anti*-β-hydroxycarboxyl moieties are not common products of such reactions.

21 M. Mulzer, B. T. Whiting and G. W. Coates, *J. Am. Chem. Soc.*, 2013, **135**, 10930.

22 For a review of asymmetric catalysts bearing 2,2′-diamino-1,1′-binaphthalene (DABN) based ligands, see: C.-M. Che and J.-S. Huang, *Coord. Chem. Rev.*, 2003, **242**, 97. For asymmetric catalysts ligated with *ortho*-aryl salicylaldehydes bridged by DABN, see: (*a*) M. Shi and C.-J. Wang, *Tetrahedron: Asymmetry*, 2002, **13**, 2161; (*b*) G.-M. Chen, F.-H. Chen and C.-H. Zhou, *Chem. Res. Chin. Univ.*, 1995, **16**, 216.

23 For reviews see: (*a*) H. B. Kagan, *Tetrahedron*, 2001, **57**, 2449; (*b*) J. R. Dehli and V. Gotor, *Chem. Soc. Rev.*, 2002, **31**, 365; (*c*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974; (*d*) R. R. Kumara and H. B. Kagan, *Adv. Synth. Catal.*, 2010, **352**, 231; (*e*) L. C. Miller and R. Sarpong, *Chem. Soc. Rev.*, 2011, **40**, 4550.

24 For related examples see: (*a*) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2001, **40**, 930; (*b*) M. Pineschi, F. D. Moro, P. Crotti, V. Di Bussolo and F. Macchia, *J. Org. Chem.*, 2004, **69**, 2099; (*c*) A. Gansäuer, C.-A. Fan, F. Keller and J. Keil, *J. Am. Chem. Soc.*, 2007, **129**, 3484; (*d*) B. Wu, J. R. Parquette and T. V. RajanBabu, *Science*, 2009, **326**, 1662; (*e*) R. Webster, C. Böing and M. Lautens, *J. Am. Chem. Soc.*, 2009, **131**, 444.

25 For example, the reaction of (*R*)-**1b** with *trans*-2,3-octene oxide under standard reaction conditions gave less than 25% conversion after 12 hours, and none of the lactones detected at that point showed an ee of greater than 80% (GC analysis). Consequently, *trans*-epoxides as substrates were not pursued further.

26 M. Mulzer and G. W. Coates, manuscript in preparation.

27 D. A. Evans, J. M. Janey, N. Magomedov and J. S. Tedrow, *Angew. Chem., Int. Ed.*, 2001, **40**, 1884.

28 For an example see: T. Kurahashi, K. Oda, M. Sugimoto, T. Ogura and H. Fujii, *Inorg. Chem.*, 2006, **45**, 7709.

29 See ESI† for further details.

30 (*a*) H. Kogen, T. Kiho, M. Nakayama, Y. Furukawa, T. Kinoshita and M. Inukai, *J. Am. Chem. Soc.*, 2000, **122**, 10214; (*b*) T. Kiho, M. Nakayama, K. Yasuda, S. Miyakoshi, M. Inukai and H. Kogen, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2315; (*c*) T. Kiho, M. Nakayama, K. Yasuda, S. Miyakoshi, M. Inukai and H. Kogen, *Bioorg. Med. Chem.*, 2004, **12**, 337; (*d*) For two non-aldol routes, see: F. Sarbia, S. Chammaa and C. García-Ruiz, *J. Org. Chem.*, 2011, **76**, 2132.