This item was submitted to [Loughborough's Research Repository](#) by the author.
Items in Figshare are protected by copyright, with all rights reserved, unless otherwise indicated.

Catalytic asymmetric crotylation of aldehydes: application in total synthesis of (–)-elisabethadione

PLEASE CITE THE PUBLISHED VERSION

<http://dx.doi.org/10.1002/chem.201500176>

PUBLISHER

© Wiley-VCH Verlag GmbH & Co

VERSION

AM (Accepted Manuscript)

PUBLISHER STATEMENT

This work is made available according to the conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) licence. Full details of this licence are available at: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

LICENCE

CC BY-NC-ND 4.0

REPOSITORY RECORD

O'Hora, Paul, Celia A. Incerti-Pradillos, Mikhail A. Kabeshov, Sergei A. Shipilovskikh, Aleksandr E. Rubtsov, Mark Elsegood, and Andrei Malkov. 2015. "Catalytic Asymmetric Crotylation of Aldehydes: Application in Total Synthesis of (–)-elisabethadione". Loughborough University. <https://hdl.handle.net/2134/16845>.

Catalytic Asymmetric Crotylation of Aldehydes: Application in Total Synthesis of (–)-Elisabethadione

Paul S. O'Hora^[a], Celia A. Incerti-Pradillos^[a], Mikhail A. Kabeshov^[a], Sergei A. Shipilovskikh^[a,b], Aleksandr E. Rubtsov^[b], Mark R. J. Elsegood^[a], and Andrei V. Malkov^{[a]*}

Abstract: A new, highly efficient Lewis base catalyst for a practical enantio- and diastereoselective crotylation of unsaturated aldehydes with *E*- and *Z*-crotyltrichlorosilanes has been developed. The method was employed as a key step in a novel asymmetric synthesis of bioactive serrulatane diterpene (–)-elisabethadione. Other strategic reactions for setting up the stereogenic centers included anionic oxy-Cope rearrangement and cationic cyclization. The synthetic route relies on simple, high yielding reactions and avoids use of protecting groups or chiral auxiliaries.

Secondary metabolites isolated from marine soft coral *Pseudopterogorgia elisabethae* exhibit a wide range of useful biological properties, which include anti-tubercular, anti-inflammatory, antimicrobial and cytotoxic activities,^[1] while partially purified gorgonian extracts are used in commercial skin care products.^[2] Selected representatives (1–4) of this family of marine natural products are shown in Figure 1.

Potent biological activity and the relatively simple structures of serrulatane diterpenes 1, 2 and other analogues, augmented by the low abundance and scarcity of supply of these compounds from their natural sources, make them attractive synthetic targets for exploring their therapeutic potential.^[3–6] However, the lack of functional groups near the stereogenic centres represents a significant challenge for stereoselective synthesis.

Figure 1. Selected *Pseudopterogorgia elisabethae* secondary metabolites.

Our novel, general strategy for setting up the stereogenic centers at C-1, C-4 and C-11 of the serrulatane skeleton relies on enantioselective crotylation of aldehyde 8 to give *syn*-alcohol 7 followed by stereoselective anionic oxy-Cope rearrangement (AOC)^[7] and ensuing cationic cyclization^[8] (Scheme 1). Importantly, the α -methyl of the cinnamyl fragment and the *syn* configuration of the homoallylic alcohol 7 play a crucial role in assuring an efficient transfer of chirality during the AOC rearrangement. Of the two possible chair-like transition structures A and B, the TS B is disfavored due to the 1,3-pseudoaxial clash. Additionally, the TS A results in *E* alkene 6, which keys in a formal 6-*endo* cyclization to afford the desired 1,4-*trans* tetralin 5, as shown by Casey and co-workers.^[8c]

Scheme 1. Retrosynthetic analysis of serrulatane diterpenes.

The success of the strategy relies on the crotylation step (8 → 7, Scheme 1), by which chirality is introduced into the molecule. Herein, we present development of an efficient, practical and scalable method for catalytic asymmetric crotylation of unsaturated aldehydes, which is then successfully applied in the enantioselective total synthesis of serrulatane diterpene 2 from the respective α -methyl cinnamaldehyde 8 (Scheme 1).

Despite recent advances in the development of catalytic asymmetric allylation of carbonyl compounds with B- and Si-based allyl reagents,^[9] including contribution from our group,^[10] the related crotylation methodology remains a challenging problem and is still dominated by stoichiometric chiral B^[11] and Si^[12] reagents. The elegant catalytic method for crotylation of aldehydes or alcohols with butadiene reported by Krische^[13] looks appealing but it does not match the enantio- and diastereoselectivity level shown by the Type I boron and silicon reagents.^[14] Brønsted acid catalyzed addition of commercial *E*-

[a] Dr. P. S. O'Hora, Dr. C. A. Incerti-Pradillos, Dr. M. A. Kabeshov, S. A. Shipilovskikh, Dr. M. R. J. Elsegood and Prof. Dr. A. V. Malkov
Department of Chemistry
Loughborough University
Loughborough, LE11 3TU, UK
Fax: +44 (0)1509 22 3925
E-mail: A. Malkov@lboro.ac.uk

[b] S. A. Shipilovskikh and Dr. A. E. Rubtsov
Department of Chemistry
Perm State University
Bukireva 15, Perm, 614990, Russia

and Z-crotylboronates to aldehydes represented a viable option,^[15] however due to their relatively high cost and uninspiring preliminary attempts^[16] our focus centered on a Lewis base catalyzed addition of easy to synthesize crotyltrichlorosilanes **Z-9a** and **E-9b** to unsaturated aldehydes.^[17] It is well documented that chiral bipyridine-*N,N'*-dioxides are highly efficient catalysts for asymmetric allylation of aldehydes with allyltrichlorosilanes.^[18] However, none of these catalysts are commercially available and their syntheses either involve lengthy sequences or give low overall yield, which makes them unsuitable for larger scale applications. Therefore, we now designed a new axially chiral bis-*N*-oxide **10** that can be synthesized in just 4 easy steps from inexpensive starting materials (Scheme 2).

Synthesis of **10** commenced with preparation of the Kröhnke salt **12** by iodination of ketone **11** in pyridine (yield 73%).^[10g] Kröhnke annulation of **12** with commercial (*R*)-myrtenal **13** in formamide in the presence of AcONH₄ produced isoquinoline **14** (yield 76%), which was converted to the respective *N*-oxide **15** by treatment with *m*CPBA (yield 94%). In the final step, an oxidative coupling^[19] of **15** produced (–)-**10** as a single distereoisomer. Using 1 equiv. of LDA, **10** was commonly isolated in 30–35% yield together with ~50% of the unreacted **15**. Thus, based on the recovered starting material, the yield of **10** in this protocol is 60–70%. The absolute configuration of the catalyst has not been rigorously established but assumed to be as shown in Scheme 2 by comparison with literature data.^[18h] For the new catalysts **10**, we propose the acronym MAKDIOX (includes initials of the co-author who developed its synthesis).

Scheme 2. Synthesis of (–)-**10** (Ar = 3,5-(CF₃)₂-C₆H₃).

The efficacy of the new catalyst **10** was assessed in the asymmetric crotylation of model aldehydes **16a–f** with crotyltrichlorosilanes **Z-9a** and **E-9b** (Table 1). Bis-*N*-oxide **10** turned out to be an extremely efficient catalyst producing excellent enantio- and diastereoselectivities over a whole range of aldehydes tested. Brief screening of solvents identified dichloromethane as the optimal choice; propionitrile came close second, while THF gave only modest enantioselectivities. Catalysts **10** proved particularly efficient with unsaturated aldehydes **16d–f** (entries 7–14), though with aliphatic **16g**

enantioselectivity dropped (entry 15) representing a common trend in the catalytic allylation with allyltrichlorosilanes.^[18] Diastereoselectivity generally reflected the geometrical purity of the starting crotyltrichlorosilanes **Z-9a** (*Z/E* 98:2) and **E-9b** (*E/Z* 95:5). However, in propionitrile cinnamyl aldehydes **16d** and **16e** appeared to react slightly faster with **Z-9a** giving the *syn*-enriched alcohols **17d** and **17e**, respectively (entries 8, 11).

Table 1. Catalytic asymmetric crotylation of aldehydes.^[a]

Entry	16	9a/9b	Solvent	Yield (%) ^d	17/18 (%) ^[b]	ee (%) ^[c]
1	16a	9a	DCM	94	98:2	92
2	16a	9b	DCM	91	4:96	96
3	16b	9a	DCM	86	98:2	92
4	16b	9b	DCM	81	4:96	96
5	16c	9a	DCM	93	95:5	85
6	16c	9b	DCM	89	5:95	91
7	16d	9a	DCM	83	98:2	95
8	16d	9a	EtCN	83	99:1	94
9	16d	9b	DCM	89	5:95	98
10	16e	9a	DCM	92	98:2	98
11	16e	9a	EtCN	92	99:1	97
12	16e	9b	DCM	88	3:97	99
13	16f	9a	DCM	80	98:2	98
14	16f	9b	DCM	82	4:96	96
15	16g	9b	DCM	55	4:96	50
16	16h	9a	EtCN	85	99:1	97
17 ^[d]	16h	9a	EtCN	82	99:1	94

[a] Unless stated otherwise, the reactions were carried out on a 0.5 mmol scale at –60 °C for 24 h with 2 mol% loading of (–)-**10**, 1.7 eq of **Z-9a** (*Z/E* 98:2) or **E-9b** (*E/Z* 95:5) and 2.0 eq of *i*Pr₂EtN; [b] determined by ¹H NMR or GC from the crude mixture; [c] ee of the major isomer, the absolute configuration is (1*R*,2*S*) for **17** and (1*R*,2*R*) for **18** (see Supporting Information); [d] the reaction was carried out on a 5 mmol scale, for 48 h.

Therefore, the asymmetric allylation of aldehyde **16h** required for the total synthesis of **2** with **Z-9a** was carried out in propionitrile. At 0.5 mmol scale the reaction afforded *syn*-

homoallylic alcohol **17h** in 85% yield and 97% ee (entry 16). Importantly, applying the same reaction conditions to a larger 5 mmol scale, excellent yield and enantioselectivity retained (yield 82%, ee 94%, entry 17) paving the way for the asymmetric synthesis of **2**.

To progress with the total synthesis, enantiopure alcohol (–)-**17h** was subjected to the AOC rearrangement using excess KH and 1 equiv. of 18-crown-6 in DME at 40 °C for 5 h (Scheme 3). Stereogenic center C-4 in **20** is created during the rearrangement, whereas C-11 is formed upon protonation of enolate **19**.^[20] After a brief optimization of the quenching conditions, the best results were achieved by cooling the reaction mixture to –78 °C, followed by a quick addition of MeOH. In this way, **20** was obtained with dr 3:1. To minimize manipulation of the oxidation-prone aldehyde and to avoid epimerization at C-11, crude **20** was subjected to Horner–Wadsworth–Emmons alkenylation conditions^[21] using phosphonate **21**. The corresponding α,β -unsaturated ester **22** was obtained in 84% yield over 2 steps (dr 3:1). The diastereoisomers were not separable at this stage and the synthesis was continued with the mixture.

The final stereogenic centre C-1 was installed through the cationic cyclization of **22** upon treatment with MeSO₃H to afford the tetralin derivative **23** (Scheme 4). Importantly, the reaction proceeded with high stereoselectivity giving only the trans isomer (dr > 25:1) in 84% yield, as evidenced by 1H NMR spectroscopy.

Scheme 3. Anionic oxy-Cope rearrangement of (–)-**17g**.

Next, hydrogenation of the double bond in **23** using H-Cube (10% Pd/C) followed by reduction of the ester with DIBAL-H afforded primary alcohol **24** as a 3:1 mixture of C-11 isomers in 84% overall yield. At this point, the isomers showed slightly different R_f values on TLC but gave a clear baseline separation on an analytical HPLC column. Therefore, separation of 500 mg of the mixture was successfully accomplished by preparative HPLC to furnish pure (–)-**24** (dr 20:1). Since this intermediate was employed by Davies and co-workers^[4,5g] in their synthesis of compounds **2–4**, it marks the formal total syntheses of all these secondary metabolites.^[22]

To complete the synthesis of (–)-**2**, alcohol (–)-**24** was oxidized to the respective aldehyde using Dess–Martin periodinane (DMP) followed by Wittig alkenylation to afford (–)-**25**. Next, as a possible shortcut to (–)-elisabethadione **2**, a one-pot sequence involving demethylation of (–)-**25** with BBr₃ followed by aerobic oxidation was examined.^[8e] A clean demethylation did take place but it was accompanied by hydrobromination of the double bond. All attempts to eliminate HBr from this product led to extensive decomposition.

Scheme 4. Completion of the total synthesis of (–)-elisabethadione **2**.

Therefore, the synthesis continued along the route described by Davies.^[4] Partial deprotection of (–)-**25** using EtSLi yielded the corresponding bisphenol **26** in 68% yield. Importantly, in the racemic variant of the synthesis, compound **26**, obtained as a 2:1 mixture of isomers, gave crystals suitable for X-ray crystallographic analysis,^[23] which confirmed the assigned relative configuration of the major isomer (Figure 2) and also showed that the two isomers differ only by the configuration at C-11.

Figure 2. Crystal structure of **26** and *epi*-**26** highlighting relative stereochemistry. The isomers differ only by the position of C(18) and H(11) on C(11), manifested by disorder at C(11).

In the endgame, bisphenol **26** was first oxidized to the respective *ortho*-quinone by CAN, followed by treatment with TsOH in benzene to afford (–)-elisabethadione **2** (dr 20:1, 20% yield from alcohol (–)-**24**), the enantiomer of the natural product. The synthesized compound exhibited $[\alpha]_D = -267$ (c 0.16, CHCl₃), opposite in sign but closely matching the absolute value reported by Davies: $[\alpha]_D = +278$ (c 0.58, CHCl₃).^[4] Other spectral data were also identical to those reported in literature.^[4] In conclusion, we developed a new bis-*N*-oxide catalyst for a scalable, highly enantioselective crotylation of unsaturated aldehydes with *E*- and *Z*-crotyltrichlorosilanes. Salient features of the new catalyst are: (i) the synthesis involves four easy steps from inexpensive, commercially available starting materials and is amendable to scale up; (ii) the new protocol is highly stereoselective and does not require chiral resolution or separation of diastereoisomers. The enantioselective crotylation method plays a pivotal role in a novel strategy for assembling the structural core of serrulatane diterpenes, which was illustrated by the asymmetric total synthesis of *ent*-elisabethadione **2**, a member of the *Pseudopterogorgia elisabethae* family of bioactive marine natural products. Other key steps to install the challenging stereogenic centers include anionic oxy-Cope rearrangement and cationic cyclization. The synthetic route relies on simple, high yielding reactions and avoids use of protecting groups or chiral auxiliaries. A more detailed investigation into the scope of the catalytic asymmetric crotylation and development of new synthetic applications are currently underway.

Acknowledgements

We thank the Leverhulme Trust for the Research grant F00 261AD and LU for studentships to POH and CAIP.

Keywords: allylation • asymmetric catalysis • rearrangement • stereoselectivity • total synthesis

- [1] a) S. A. Look, W. Fenical, G. K. Matsumoto, J. Clardy, *J. Org. Chem.* **1986**, *51*, 5140–5145; b) A. D. Rodríguez, C. Ramirez, *Org. Lett.* **2000**, *2*, 507–510; c) A. D. Rodríguez, C. Ramirez, *J. Nat. Prod.* **2001**, *64*, 100–102; d) A. Ata, R. G. Kerr, C. E. Moya, R. S. Jacobs, *Tetrahedron* **2003**, *59*, 4215–4222; e) T. J. Heckrodt, J. Mulzer, *Top. Curr. Chem.* **2005**, *244*, 1–41; f) X. Dai, Z. Wan, R. G. Kerr, H. M. L. Davies, *J. Org. Chem.* **2007**, *72*, 1895–1900; g) F. Berrue, R. G. Kerr, *Nat. Prod. Rep.* **2009**, *26*, 681–710;
- [2] A. Kijjoa, P. Sawanwong, *Mar. Drugs* **2004**, *2*, 73–82.
- [3] For the total syntheses of **1**, see: a) R. R. Cesati, III, J. De Armas, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 96–101; b) H. M. L. Davies, A. M. Walji, *Angew. Chem. Int. Ed.* **2005**, *44*, 1733–1735; c) J. S. Yadav, A. K. Basak, P. Srihari, *Tetrahedron Lett.* **2007**, *48*, 2841–2843; d) T. G. Elford, S. Nave, R. P. Sonawane, V. K. Aggarwal, *J. Am. Chem. Soc.* **2011**, *133*, 16798–16801; e) J. S. Yadav, B. Thirupathaiah, A. Al Khazim Al Ghamdi, *Eur. J. Org. Chem.* **2012**, 2072–2076. For the formal total synthesis of **1**, see: f) M. Harmata, X. Hong, *Tetrahedron Lett.* **2005**, *46*, 3847–3849.
- [4] For the total syntheses of **2**, see: H. M. L. Davies, X. Dai, *Tetrahedron* **2006**, *62*, 10477–10484 and ref [1e].
- [5] For the total syntheses of **3** and **4**, see: a) K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein, R. Kranich, *Angew. Chem. Int. Ed.* **2001**, *40*, 2482–2486; b) K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein, R. Kranich, *Chem. Eur. J.* **2001**, *7*, 5359–5371; c) A. I. Kim, S. D. Rychnovsky, *Angew. Chem. Int. Ed.* **2003**, *42*, 1267–1270; d) N. Waizumi, A. R. Stankovic, V. H. Rawal, *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023; e) D. C. Harrowven, D. D. Pascoe, D. Demurtas, H. O. Bourne, *Angew. Chem. Int. Ed.* **2005**, *44*, 1221–1222; f) A. A. Boezio, E. R. Jarvo, B. M. Lawrence, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6046–6050; g) H. M. L. Davies, X. Dai, M. S. Long, *J. Am. Chem. Soc.* **2006**, *128*, 2485–2490. For the formal total synthesis of **3** and **4**, see: h) J. Preindl, C. Leitner, S. Baldauf, J. Mulzer, *Org. Lett.* **2014**, *16*, 4276–4279.
- [6] For selected examples of total syntheses of other serrulatane diterpenes, see a) A. Majdalani, H.-G. Schmalz, *Synlett* **1997**, 1303–1305; b) T. Geller, H.-G. Schmalz, J. W. Bats, *Tetrahedron Lett.* **1998**, *39*, 1537–1540; c) F. Dehmel, J. Lex, H.-G. Schmalz, *Org. Lett.* **2002**, *4*, 3915–3918; d) J. M. H. Lu, M. V. Perkins, H. J. Greisser, *Tetrahedron*, **2013**, *69*, 6468–6473.
- [7] For the most relevant examples of the AOC rearrangement, see a) L. A. Paquette, C. A. Teleha, R. T. Taylor, G. D. Maynard, R. D. Rogers, J. C. Gallucci, J. P. Springer, *J. Am. Chem. Soc.* **1990**, *112*, 265–277; b) L. A. Paquette, R. E. Maleczka, Jr., *J. Org. Chem.* **1991**, *56*, 912–913; c) E. Lee, I.-J. Shin, T.-S. Kim, *J. Am. Chem. Soc.* **1990**, *112*, 260–264; d) L. A. Paquette, G. D. Maynard, *Angew. Chem. Int. Ed.* **1991**, *30*, 1368–1370; e) L. A. Paquette, G. D. Maynard, *J. Am. Chem. Soc.* **1992**, *114*, 5018–5027; f) K. Tomooka, S.-Y. Wie, T. Nakai, *Chem. Lett.* **1991**, *20*, 43–46.
- [8] For the most relevant examples of cationic cyclizations, see a) E. J. Corey, S. E. Lazerwith, *J. Am. Chem. Soc.* **1998**, *120*, 12777–12782; b) J. P. Davidson, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 13486–13489; c) R. Appelbe, M. Casey, A. Dunne, E. Pascarella, *Tetrahedron Lett.* **2003**, *44*, 7641–7644; d) K. Surendra, G. Rajendar, E. J. Corey, *J. Am. Chem. Soc.* **2013**, *135*, 13486–13489; e) J. Deng, R. Li, Y. Luo, J. Li, S. Zhou, Y. Li, J. Hu, A. Li, *Org. Lett.* **2013**, *15*, 2022–2025.
- [9] For recent overviews, see a) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2794; b) J. W. J. Kennedy, D. G. Hall, *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739; c) M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774–7854.
- [10] a) A. V. Malkov, L. Dufková, L. Farrugia, P. Kočovský, *Angew. Chem.* **2003**, *115*, 3802–3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3674–3677; b) A. V. Malkov, M. Bell, F. Castelluzzo, P. Kočovský, *Org. Lett.* **2005**, *7*, 3219–3222; c) A. V. Malkov, P. Ramírez-López, L. Biedermannová, L. Rulišek, L. Dufková, M. Katora, F. Zhu, P. Kočovský, *J. Am. Chem. Soc.* **2008**, *130*, 5341–5348; d) A. V. Malkov, M. A. Kabeshov, M. Bartóg, P. Kočovský, *Chem. Eur. J.* **2009**, *15*, 1570–1573; e) A. V. Malkov, M. Bartóg, Y. Jewkes, J. Mikušek, P. Kočovský, *J. Org. Chem.* **2011**, *76*, 4800–4804; f) A. V. Malkov, O. Kysilka, M. Edgar, A. Kadličková, M. Katora, P. Kočovský, *Chem. Eur. J.* **2011**, *17*, 7162–7166; g) A. V. Malkov, S. Stončius, M. Bell, F. Castelluzzo, P. Ramírez-López, L. Biedermannová, V. Langer, L. Rulišek, P. Kočovský, *Chem. Eur. J.* **2013**, *19*, 9167–9185.
- [11] a) H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093; b) H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 293–294; c) B. Kim, J. Garcia, S. Masamune, *J. Org. Chem.* **1987**, *52*, 4831–4832; d) R. P. Short, S. Masamune, *J. Am. Chem. Soc.* **1989**, *111*, 1892–1894; e) E. J. Corey, C. Yu, S. S. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496; f) W. R. Roush, A. E. Walts, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190; g) W. R. Roush, A. D. Palkowitz, K. Ando, *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359; h) W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterman, *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348; i) E. Canales, K. G. Prasad, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573.
- [12] a) H. Kim, S. Ho, J. L. Leighton, *J. Am. Chem. Soc.* **2011**, *133*, 6517–6520; b) L. M. Suen, M. L. Steigerwald, J. L. Leighton, *Chem. Sci.* **2013**, *4*, 2413–2417.
- [13] a) J. R. Zbieg, E. Yamaguchi, E. L. McInturff, M. J. Krische, *Science*, **2012**, *336*, 324–327; b) E. L. McInturff, E. Yamaguchi, M. J. Krische, *J.*

- Am. Chem. Soc.* **2012**, *134*, 20628–20631.
- [14] S. E. Denmark, E. J. Weber, *Helv. Chim. Acta*, **1983**, *66*, 1655–1660.
- [15] a) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661; b) V. Rauniyar, D. G. Hall, *Angew. Chem.* **2006**, *118*, 2486–2488; *Angew. Chem. Int. Ed.* **2006**, *45*, 2426–2428; c) V. Rauniyar, H. Zhai, D. G. Hall, *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490; d) P. Jain, J. C. Antilla, *J. Am. Chem. Soc.* **2010**, *132*, 11884–11886; e) C. A. Incerti-Pradillos, M. A. Kabeshov, A. V. Malkov, *Angew. Chem. Int. Ed.* **2013**, *52*, 5338–5341; f) T. Miura, Y. Nishida, M. Morimoto, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 11497–11500; g) P. Motloch, I. Valterová, M. Kotora, *Adv. Synth. Catal.* **2014**, *356*, 199–204; h) F. Hessler, A. Korotvička, D. Nečas, I. Valterová, M. Kotora, *Eur. J. Org. Chem.* **2014**, 2543–2548.
- [16] At 0.5 mmol scale, crotylation of **16g** with Z-crotylboronic acid pinacol ester using chiral phosphoric acid (*R*)-TRIP (10 mol%), refs [14d, 14e], produced alcohol **17g** in 78% yield and 90% ee. However, at a larger 5 mmol scale, under the same conditions, the reaction turned sluggish and was accompanied by a substantial drop in enantioselectivity (40% ee).
- [17] Isomerically enriched **9a** and **9b** are routinely synthesized in our laboratory on a 10 g scale by adapting the following protocols: a) J. Tsuji, M. Hara, K. Ohno, *Tetrahedron* **1974**, *30*, 2143–2146; b) M. Kira, T. Hino, H. Sakurai, *Tetrahedron Lett.* **1989**, *30*, 1099–1102; c) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 3513–3526. For details, see Supporting Information.
- [18] a) M. Nakajima, M. Saito, M. Shiro, S. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420; b) T. Shimada, A. Kina, S. Ikeda, T. Hayashi, *Org. Lett.* **2002**, *4*, 2799–2801; c) T. Shimada, A. Kina, T. Hayashi, *J. Org. Chem.* **2003**, *68*, 6329–6337; d) R. Hrdina, I. Valterová, J. Hodačová, I. Císařová, M. Kotora, *Adv. Synth. Catal.* **2007**, *349*, 822–826; e) A. V. Malkov, M.-M. Westwater, A. Gutnov, P. Ramírez-López, F. Friscourt, A. Kadlčíková, J. Hodačová, Z. Rankovic, M. Kotora, P. Kočovský, *Tetrahedron* **2008**, *64*, 11335–11348; f) R. Hrdina, M. Dračinský, I. Valterová, J. Hodačová, I. Císařová, M. Kotora, *Adv. Synth. Catal.* **2008**, *350*, 1449–1456; g) A. Kadlčíková, R. Hrdina, I. Valterová, M. Kotora, *Adv. Synth. Catal.* **2009**, *351*, 1279–1283; h) A. Kadlčíková, I. Valterová, L. Ducháčková, J. Roithová, M. Kotora, *Chem. Eur. J.* **2010**, *16*, 9442–9445.
- [19] a) R. A. Abramovitch, J. Campbell, E. E. Knaus, A. Silhankova, *J. Heterocycl. Chem.* **1972**, *9*, 1367–1371; b) Y. Tagawa, K. Hama, Y. Goto, M. Hamana, *Heterocycles* **1992**, *34*, 2243–2246; c) S. E. Denmark, Y. Fan, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 687–707; d) O. N. Chupakhin, I. A. Utepova, M. V. Varaksin, E. V. Tretyakov, G. V. Romanenko, D. V. Stass, V. I. Ovcharenko, *J. Org. Chem.* **2009**, *74*, 2870–2872; e) I. S. Kovalev, V. L. Rusinov, O. N. Chupakhin, *Chem. Heterocycl. Compd.*, **2009**, *45*, 176–181.
- [20] In model studies using homoallylic alcohol derived from simple α -methyl cinnamaldehyde, variation of quenching conditions resulted in diastereomeric ratios between 3:1 and 1:2.
- [21] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essensfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
- [22] Overall, alcohol (–)-**24** was synthesized in 10 steps from 1,3,4-trimethoxybenzene. Davies and co-workers (refs 4,5g) obtained (+)-**24** from the same starting material in the same number of steps but through a different set of reactions.
- [23] Crystal Data for **26**: $C_{21}H_{32}O_3$, $M_r = 332.46$, $0.86 \times 0.60 \times 0.04 \text{ mm}^3$, monoclinic, $P2_1/c$, $a = 18.179(3)$, $b = 7.3992(10)$, $c = 14.334(2) \text{ Å}$, $\beta = 99.856(2)^\circ$, $V = 1899.6(5) \text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.162 \text{ Mg m}^{-3}$, $\mu(\text{Mo-K}\alpha) = 0.08 \text{ mm}^{-1}$, $\lambda = 0.71073 \text{ Å}$, $T = 150 \text{ K}$, $2\theta_{\text{max}} = 61.2^\circ$, 21151 data measured, 5734 independent reflections, $R_{\text{int}} = 0.035$, $R[F^2 > 2\sigma(F^2)]$, 4047 data = 0.049, $wR[F^2, \text{all data}] = 0.143$, residual electron density within $\pm 0.52 \text{ e Å}^{-3}$. For details, see Supporting Information.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

A new catalyst for a practical and scalable enantio- and diastereoselective crotylation of unsaturated aldehydes has been developed. The method was employed as a key step in a novel asymmetric route to bioactive serrulatane diterpene (-)-elisabethadione. Other strategic reactions for setting up the stereogenic centers included anionic oxy-Cope rearrangement and cationic cyclization.

Paul S. O'Hora, Celia A. Incerti-Pradillos, Mikhail A. Kabeshov, Sergei A. Shipilovskikh, Aleksandr E. Rubtsov, Mark R. J. Elsegood, and Andrei V. Malkov*

Page No. – Page No.

Catalytic Asymmetric Crotylation of Aldehydes: Application in Total Synthesis of (-)-Elisabethadione