Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2020, **11**, 4125

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 20th January 2020
Accepted 27th March 2020

DOI: 10.1039/d0sc00377h

rsc.li/chemical-science

Enantiomerically enriched tetrahydropyridine allyl chlorides†

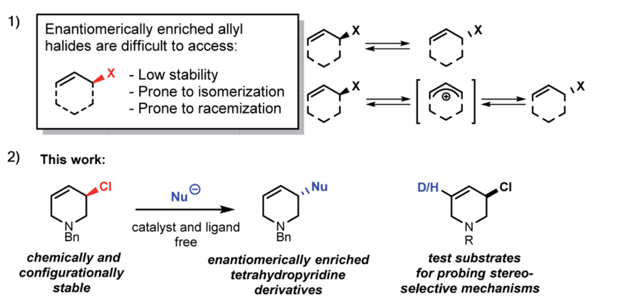
Sedef Karabiyikoglu,[a] Alexandre V. Brethomé,[a] Thomas Palacin,[a] Robert S. Paton*[b] and Stephen P. Fletcher*[a]

Enantiomerically enriched allyl halides are rare due to their configurational lability. Here we report stable piperidine-based allyl chloride enantiomers. These allyl chlorides can be produced *via* kinetic resolution, and undergo highly enantiospecific catalyst-free substitution reactions with C, N, O and S-based nucleophiles. DFT calculations and experiments with deuterium-labelled chloro-tetrahydropyridine, selectively prepared using H/D primary kinetic isotope effect, were used to investigate the mechanisms of resolution and substitution reactions. The allyl chlorides may also serve as valuable mechanistic tools for probing stereoselective reaction pathways.

Introduction

The stereoselective synthesis of molecules with chloro-substituted stereogenic centres is challenging. Despite considerable effort, few asymmetric chlorination methods have been reported.[1–3] Synthesis of enantiomerically enriched allyl halides has proven to be especially difficult as they are generally prone to fast isomerization and racemization (Scheme 1(1)).[4]

Enantioenriched allyl chlorides are virtually unknown, except as a feature of diastereomeric compounds, where other stereogenic elements exert control over the observed stable allyl halide configuration.[2d,5] The selective preparation of enantiomerically enriched allyl chlorides[5a] could be important as stereogenic centres containing C–Cl bonds are found in pharmaceuticals,[5b,6] and the allyl halides may undergo stereospecific reactions.[1,6,7]



Scheme 1 Properties of allyl halide enantiomers and this work.

Tetrahydropyridines (THPs) are a subgroup of nitrogen heterocycles found in biologically active molecules.[8] THPs are also important precursors to functionalized piperidines. Piperidine is among the most common motifs found in licensed pharmaceuticals,[8a] and is frequently found in best-selling brand-name medicines.[9,10] 3-substituted piperidine derivatives are at the core of many potent therapeutic agents (Fig. 1),[9,11,12] and methods for their preparation have attracted growing attention.[13] However, asymmetric syntheses of 3-substituted piperidines *via* direct functionalization is scarce.[14]

Results and discussion

Due to the importance of THPs, racemic 3-chloro-1,2,3,6-tetrahydropyridines were examined in asymmetric allylic additions (AAAs) with Zr-nucleophiles and copper catalysts. To our surprise, we were able to isolate enantiomerically enriched allyl chlorides from the reaction mixture. The kinetic resolution of

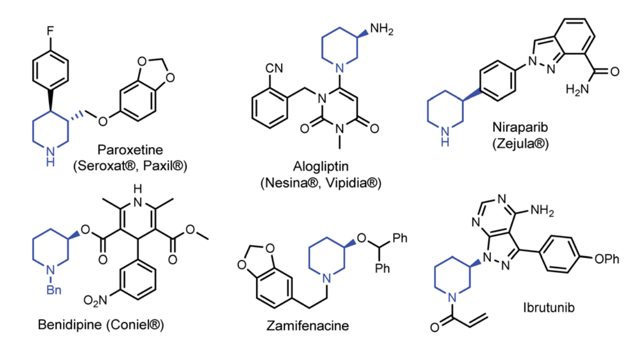


Fig. 1 Examples of biologically active 3-substituted piperidines.

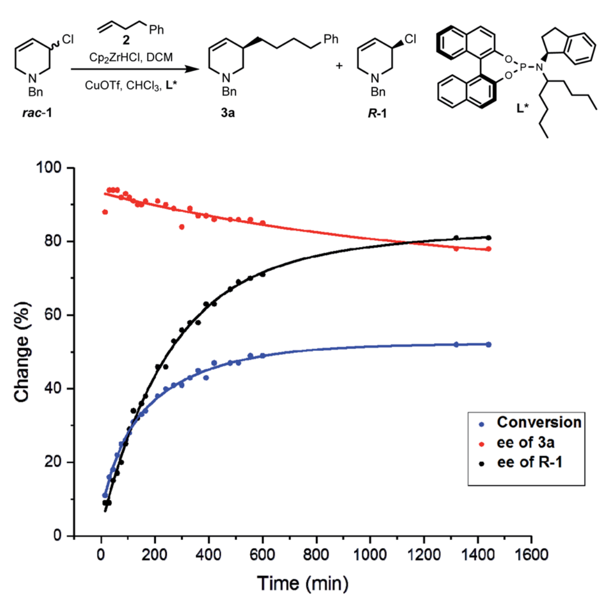
[a]Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK. E-mail: stephen.fletcher@chem.ox.ac.uk
[b]Department of Chemistry, Colorado State University Fort Collins, Colorado 80523, USA. E-mail: robert.paton@colostate.edu

† Electronic supplementary information (ESI) available: Additional experimental details and spectral data. See DOI: 10.1039/d0sc00377h

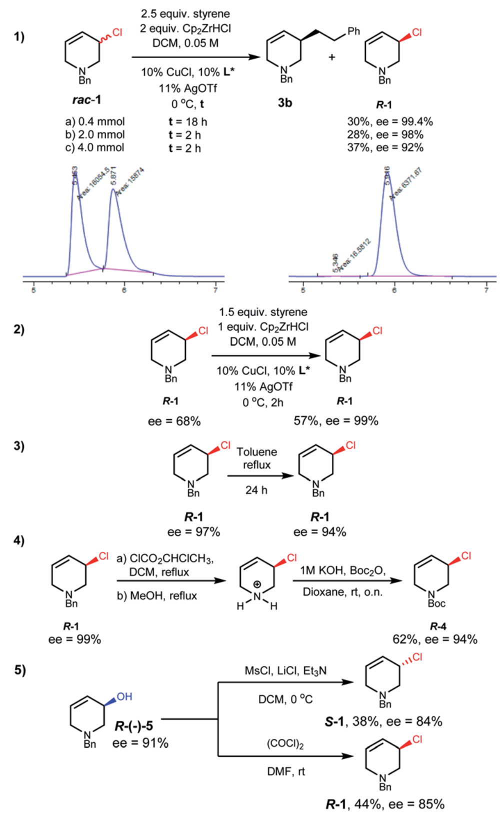
halides has received little attention,[2e,15] with resolution of allyl halides being limited to a single report of activated allyl fluorides.[16] Here we report the synthesis of enantioenriched allylic 3-chloro-THPs *via* kinetic resolution and investigate alternative preparation methods. The chemically and configurationally stable allyl chlorides can be used to prepare a wide range of THP derivatives that may be useful in synthesis and medicinal chemistry (Scheme 1(2)).

Initial exploration[17] of Cu-catalyzed AAA with chlorotetrahydropyridines showed recovery of scalemic allyl chloride, indicating slow (or indeed no) interconversion between starting material enantiomers during the reaction. The reaction of 1-benzyl-3-chloro-1,2,3,6-tetrahydropyridine (***rac*-1**) with 4-phenyl-1-butene (**2**) was followed in time (Scheme 2). After 30 minutes at −10 °C the reaction reached 16% conversion, giving product **3a** in 94% ee, with the ee of **3a** then decreasing ∼15% due to slow consumption of the less reactive starting enantiomer over time. The ee of **1** increased from 0 to 80% over 22 hours, where it remained unchanged (within experimental error).[17] Allyl chlorides bearing different protecting groups (Boc, Cbz, Ts and Ms) were tested in Cu-catalyzed AAAs with 4-phenyl-1-butene,[17] however; these reactions were low yielding and not stereoselective.

We then investigated conditions to optimize the ee of **1**.[17] With styrene, diluting the reaction conditions, and using DCM as solvent, ***R*-1** was obtained in useful yield with excellent selectivity (Scheme 3(1a)). Kinetic resolution was found to be much faster on larger scales (Scheme 3(1b and c)). These reactions also afforded alkylation product **3b** in 49–65% yield and 84–88% ee. The mass balance in these reactions is good in that neither the small nor large scale reactions of ***rac*-1** with styrene or **2** gave detectable amounts of side products. Conveniently, scalemic allylic chloride samples can be recycled, with



Scheme 2 Kinetic resolution of *rac*-1 using a copper–ligand catalyst and an alkylzirconium reagent.



Scheme 3 (1) Kinetic resolution of ***rac*-1** and HPLC traces of racemic and enantiomerically enriched **1** using a chiral non-racemic stationary phase. (2) Kinetic resolution of scalemic **1**. (3) Configurational stability of ***R*-1** to heating. (4) Removal and addition of a protecting group to give *N*-Boc protected ***R*-1** with little loss of enantiomeric excess (5) alternative synthesis of ***R*-** and ***S*-1** from an enantiomerically enriched alcohol ***R*-5** *via* selective inversion (to give ***S*-1**) or selective retention (to give ***R*-1**).

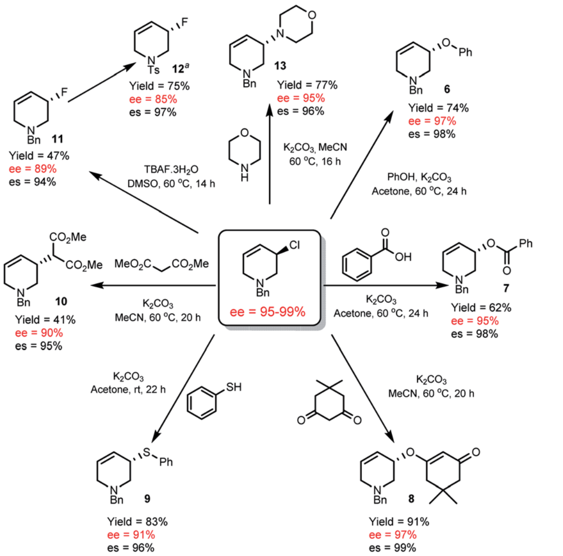
resolution on such material giving up to 99% ee using lower equiv. of alkyl-Zr reagent (Scheme 3(2)).

***R*-1** shows remarkable thermal stability; in toluene heated to reflux for 24 hours only 3% ee erosion was observed without any detectable side product formation (Scheme 3(3)). If desired the *N*-protecting group of ***R*-1** can be exchanged, for example to *N*-Boc, through a pyridinium salt intermediate with only a small decrease in ee (Scheme 3(4)).[17]

Alternative routes to enantioenriched **1** were tested (see ESI†). Enantiomerically enriched (Scheme 3(5), 91% ee) alcohol ***R*-5**, after optimization,[17] could be chlorinated with either inversion or retention, and reasonable stereospecificity, to give either enantiomer of **1**.

Though thermally stable, ***R*-1** is a versatile chiral non-racemic building block and undergoes a variety of highly stereospecific substitution reactions. Using mild conditions we were able to access a variety of THP derivatives including ethers (**6**), esters (**7**), vinylogous ethers (**8**), thioethers (**9**), malonates (**10**), fluorides (**11**) and amines (**13**) with very high stereospecificity (94–99% es, Scheme 4).

The absolute configuration of ***R*-1** was assigned[17] by converting allyl fluoride **11** to **12** (Scheme 4), which has been



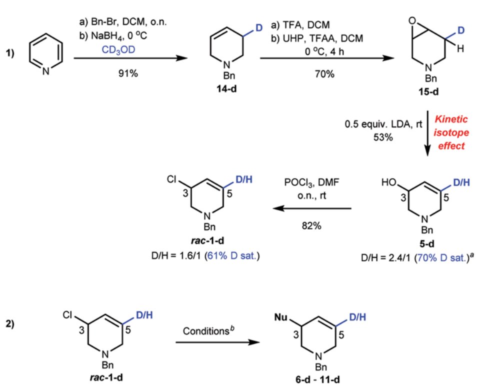
Scheme 4 Enantiospecific substitution reactions of *R*-1. es = % enantiospecificity; es = [(ee of product/ee of *R*-1) × 100]. [a]The absolute configuration of **12** is known, see ESI† for the conditions to prepare **12**.

determined by X-ray crystallographic analysis,[18] and knowledge (*vida infra*) that ***R*-1** to **11** occurs *via* an S_N2 pathway.

To clarify the mechanism of stereospecific substitution we prepared isotopically labelled ***rac*-1-d**. Reduction of benzylpyridinium bromide in CD_3OD selectively adds D to the C3 position of **14-d**, which was epoxidized to **15-d**. We used the *primary kinetic isotope effect* of H/D deprotonation[19] as a strategy to prepare deuterium-labelled allyl alcohol **5-d**. This sequence gave a 2.4 : 1 D/H ratio at C5 after optimization.[17] ***Rac*-1-d** was obtained with 61–65% D saturation as judged by ^1H and ^2H NMR spectroscopic experiments after chlorination (Scheme 5(1)).[20] *Acyclic* allyl chlorides generally undergo S_N2' substitutions as the carbon with the leaving group can freely rotate about the vicinal olefin,[21] but mechanistic studies with *cyclic* allyl chlorides suggests S_N2 substitutions are generally favoured followed by *anti*-S_N2' and *syn*-S_N2' pathways.[4e–h,22]

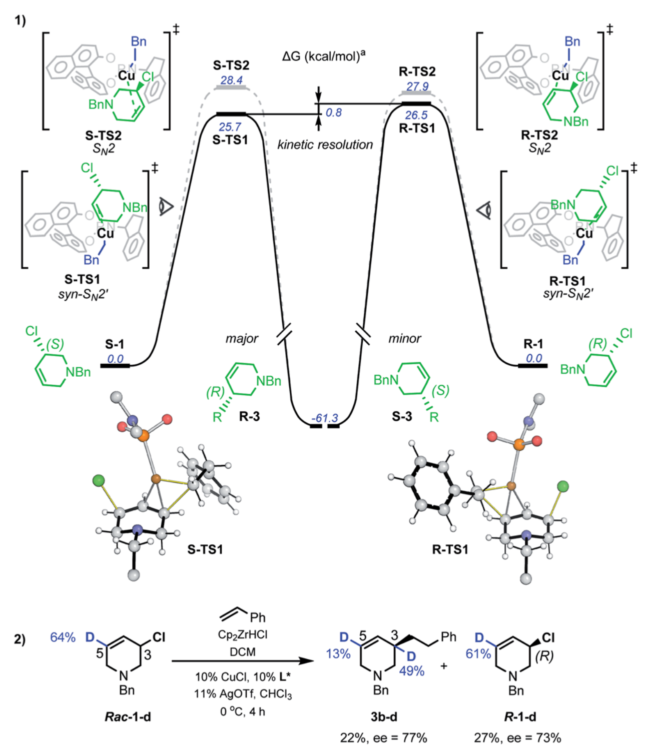
Our results (Scheme 5(2)) show that the %D saturation at C5 of ***rac*-1-d** is usually conserved throughout these substitutions, strongly suggesting S_N2 reactions. An exception to this trend is seen with thioether **9-d** which shows some D transfer to C3. As the es of ***R*-1** to **9** is high (96% es), it suggests that the reaction occurs by a mixture of pathways, in favour of S_N2, with both S_N2 and *syn*-S_N2' leading to the same enantiomer. Density Functional Theory (DFT) calculations excluded transannular aziridinium ion formation due to the large free energy difference between an azabicyclic intermediate and **1** (37.8 kcal mol^{-1}).[17] Such levels of energy necessarily imply unfavourable transition structures to access it (TS ≥ 37.8 kcal mol^{-1}), thus eliminating the possibilities of an intra-nucleophilic reaction pathway with double inversion.

DFT studies were also used to probe the kinetic resolution of ***rac*-1** (Scheme 6(1)). Geometry optimisations were carried out with M062X functional and the 6-31G(d) basis set for C, H, N, O, P, Cl atoms and the LANL2DZ effective core potential/valence double zeta basis set for Cu. Single point energy corrections were obtained at the M062X/def2-TZVPP level of theory with chloroform solvation described by an implicit Solvation Model based on Density (SMD), then corrected using D3-dispersion energy as developed by Grimme.[17]



Product	%D at C-5_{SM}	NuH	%D at C-5_{Pro}	%D at C-3_{Pro}
6-d	61%	PhOH	61%	-
7-d	65%	$PhCO_2H$	65%	-
8-d	61%	Dimedone	63%	-
9-d	64%	PhSH	50%	13%
10-d	61%	$MeO_2CCH_2CO_2Me$	60%	-
11-d	61%	TBAF	62%	-

Scheme 5 (1) Preparation of ***rac*-1-d**. [a]%D = $[n_{5\text{-d}}/(n_5 + n_{5\text{-d}})] \times 100$. (2) Mechanistic studies on substitution reactions. [b]Conditions for substitution reactions are the same as shown in Scheme 4.



Scheme 6 Mechanistic study of Cu-catalysed AAAs. [a]SMD-M062X/def2-TZVPP//M062X/6-31G(d)/LANL2DZ computed Gibbs energies at 298.15 K and 1 mol L^{-1}.

Starting from a Cu–L* complex in which the ligand *n*-alkyl groups were abbreviated in computational models,[17] ***rac*-1** can bind to the metal centre at the N lone-pair. Two diastereomeric complexes can form with similar stabilities: of which ***S*-C1** (0.8 kcal mol^{-1}) is slightly less favourable than ***R*-C1** (−0.2 kcal mol^{-1}). Such a qualitative difference could potentially suggest a role in stereoselectivity and explain the specificity observed with *N*-benzyl-protected allyl chlorides.[17] For displacement of chloride by the catalyst, five possible pathways were investigated: *syn-* and *anti-* oxidative addition, *anti*-S_N2', S_N2 and *syn*-S_N2'. Alternative conformations were considered for each possibility.[17] The *syn*-S_N2' transition structure (TS) ***S*-TS1** was the most favourable overall, proceeding from the reaction of ***S*-1** with a barrier of 25.7 kcal mol^{-1} to give the (*R*)-product of alkylation. For the (*S*)-enantiomer, this was followed by the S_N2 TS ***S*-TS2** (28.4 kcal mol^{-1}). Copper-catalyzed allylic alkylations are often described as occurring through complexation of a Cu(I) complex to the allylic olefin followed by oxidative addition to generate an allyl–Cu(III)[23] complex, but here *anti*-S_N2', *syn-* and *anti*-oxidative addition were found to be comparatively unfavourable, except with the anti-S_N2'-oxidative addition pathway (***S*-TS3**) that is only 0.1 kcal mol^{-1} higher than ***S*-TS2**.[17] Our computational model is nevertheless qualitatively correct to disfavour ***S*-TS3** over ***S*-TS2** as it would otherwise give the opposite enantiomer than observed experimentally. Similarly to ***S*-1**, ***R*-1** was found to preferentially react *via* a *syn*-S_N2' pathway, with the barrier for ***R*-TS1** at 26.5 kcal mol^{-1}. As found for ***S*-1**, the next most stable was S_N2 TS ***R*-TS2** at 27.9 kcal mol^{-1}. Based on these computations, the alkylation of ***R*-1** is kinetically disfavoured *vs.* ***S*-1** ($\Delta\Delta G^{\ddagger}_{\text{syn-S}_N2'} = 0.8$ kcal mol^{-1}) *via* dominant *syn*-S_N2' pathways for both enantiomers. This is consistent with the absolute sense of enantioenrichment observed experimentally, in which the (*R*)-enantiomer of both substrate and product accumulates. In addition to the major *syn*-S_N2' pathway, our result possibly implicate involvement of a minor S_N2 mechanism to give the same product stereochemistry.

D-labelled ***rac*-1-d** was subjected to Cu-catalyzed resolution (Scheme 6(2)), and in accordance with computation, both S_N2' and S_N2 pathways are operative: product **3b–d** shows D-incorporation at the C3 (49%) and C5 (13%) positions consistent with *syn*-S_N2' and then S_N2 being the most favourable pathways. No deuterium-isomerization of starting **1-d** was observed and ***R*-1-d** was isolated from the reaction mixture with 73% ee.

Conclusions

We have found allyl chlorides that are thermodynamically stable and can be prepared in highly enantioenriched form. A rare kinetic resolution of allylic chlorides formed piperidine-based allyl chlorides with high ee. The allyl chloride enantiomers can be separated by chromatography using a chiral non-racemic stationary phase, or prepared by stereospecific (with retention or inversion) chlorination of the corresponding alcohol. The allyl chloride undergoes highly enantiospecific substitution reactions with nucleophiles to give a wide range of tetrahydropyridine products which are important in biology and medicine. Experiments with D-labelled chloro-tetrahydropyridine and DFT calculations were used to investigate the mechanistic pathways of nucleophilic substitution and kinetic resolution reactions. This work provides new routes for the formation of enantiomerically enriched tetrahydropyridine derivatives. Further, ***rac*-1**, ***R*-** or ***S*-1**, ***R*-1-d** and other configurationally stable allyl halides may serve as probe substrates for investigating reaction pathways in mechanistic studies of reactions.[24]

Conflicts of interest

Oxford University Innovation has filed a patent application (GB1815018.5) with S. P. F. and S. K. named as inventors. The remaining authors declare no competing financial interests. A version of this manuscript has been shared and posted on ChemRxiv.

Acknowledgements

Financial support from the UK Engineering and Physical Sciences Research Council (EP/N022246/1) is gratefully acknowledged. A. V. B. is grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for a studentship, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex. T. P. thanks the People Programme (Marie Curie Actions) of the EU's Seventh Framework Programme (FP7/2007–2013) under REA grant agreement 316955 for funding. The authors thank Dr Nader Amin for assistance in D-NMR. We acknowledge the RMACC Summit supercomputer, which is supported by the National Science foundation (ACI-1532235 and ACI1532236), the University of Colorado Boulder and Colorado State University, and the Extreme Science and Engineering Discovery Environment (XSEDE) through allocation TGCHE180056.

Notes and references

1 For asymmetric α-chlorination of carbonyl compounds, see: (*a*) Y. H. Luo, Y. J. Ping, Z. R. Li, X. Gu, Z. J. Xu and C. M. Che, *Synthesis*, 2018, **50**, 1105; (*b*) X. Bao, S. Wei, L. Zou, Y. He, F. Xue, J. Qu and B. Wang, *Chem. Commun.*, 2016, **52**, 11426; (*c*) T. Sakai, S. Hirashima, K. Nakashima, C. Maeda, A. Yoshida, Y. Koseki and T. Miura, *Chem. Pharm. Bull.*, 2016, **64**, 1781; (*d*) W. Zheng, Z. Zhang, M. J. Kaplan and J. C. Antilla, *J. Am. Chem. Soc.*, 2011, **133**, 3339; (*e*) K. Shibatomi and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2008, **47**, 5796; (*f*) S. France, H. Wack, A. Taggi, A. M. Hafez, T. R. Wagerle, M. H. Shah, C. L. Dusich and T. Lectka, *J. Am. Chem. Soc.*, 2004, **126**, 4245.

2 For asymmetric chlorination of olefins, see: (*a*) U. Hennecke, *Chem.–Asian J.*, 2012, **7**, 456; (*b*) A. Castellanos and S. P. Fletcher, *Chem.–Eur. J.*, 2011, **17**, 5766; (*c*) K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch and J. S. Chen, *J. Am. Chem. Soc.*, 2011, **133**, 8134; (*d*)

S. A. Snyder, Z. Y. Tang and R. Gupta, *J. Am. Chem. Soc.*, 2009, **131**, 5744; (*e*) Y. Tan, S. Luo, D. Li, N. Zhang, S. Jia, Y. Liu, W. Qin, C. E. Song and H. Yan, *J. Am. Chem. Soc.*, 2017, **139**, 6431; (*f*) M. L. Landry, D. X. Hu, G. M. McKenna and N. Z. Burns, *J. Am. Chem. Soc.*, 2016, **138**, 5150.

3 For asymmetric aziridine ring openings with chloride salts, see: K. Ohmatsu, Y. Hamajima and T. Ooi, *J. Am. Chem. Soc.*, 2012, **134**, 8794.

4 (*a*) X. Y. Cui, Y. Ge, S. M. Tan, H. Jiang, D. Tan, Y. Lu, R. Lee and C. H. Tan, *J. Am. Chem. Soc.*, 2018, **140**, 8448; (*b*) J. Scoccia, S. J. Perez, V. Sinka, D. A. Cruz, J. M. Lopez-Soria, I. Fernandez, V. S. Martin, P. O. Miranda and J. I. Padron, *Org. Lett.*, 2017, **19**, 4834; (*c*) E. Rideau, H. You, M. Sidera, T. D. W. Claridge and S. P. Fletcher, *J. Am. Chem. Soc.*, 2017, **139**, 5614; (*d*) C. Li, Y. Zhang, Q. Sun, T. Gu, H. Peng and W. Tang, *J. Am. Chem. Soc.*, 2016, **138**, 10774; (*e*) U. K. Wefelscheid and S. Woodward, *J. Org. Chem.*, 2009, **74**, 2254; (*f*) E. W. Collington and A. I. Meyers, *J. Org. Chem.*, 1971, **36**, 3044; (*g*) H. L. Goering, T. D. Nevitt and E. F. Silversmith, *J. Am. Chem. Soc.*, 1955, **77**, 4042; (*h*) W. G. Young, S. Winstein and H. L. Goering, *J. Am. Chem. Soc.*, 1951, **73**, 1958.

5 (*a*) For the single example only applied on 1*H*-indine, see: A. Lennartson, S. Olsson, J. Sundberg and M. Hakansson, *Angew. Chem., Int. Ed.*, 2009, **48**, 3137; (*b*) F. Zhong, W. J. Yue, H. J. Zhang, C. Y. Zhang and L. Yin, *J. Am. Chem. Soc.*, 2018, **140**, 15170; (*c*) C. V. Vogel, H. Pietraszkiewicz, O. M. Sabry, W. H. Gerwick, F. A. Valeriote and C. D. Vanderwal, *Angew. Chem., Int. Ed.*, 2014, **53**, 12205.

6 (*a*) J. R. Reyes and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2016, **55**, 3077; (*b*) D. X. Hu, F. J. Seidl, C. Bucher and N. Z. Burns, *J. Am. Chem. Soc.*, 2015, **137**, 3795; (*c*) M. Oestreich, *Angew. Chem., Int. Ed.*, 2005, **44**, 2324; (*d*) H. Ibrahim and A. Togni, *Chem. Commun.*, 2004, 1147.

7 (*a*) M. Bergeron-Brlek, T. Teoh and R. Britton, *Org. Lett.*, 2013, **15**, 3554; (*b*) R. Britton and B. Kang, *Nat. Prod. Rep.*, 2013, **30**, 227.

8 (*a*) Y. Dudognon, J. Rodriguez, T. Constantieux and X. Bugaut, *Eur. J. Org. Chem.*, 2018, 2432; (*b*) C. C. Chrovian, A. Soyode-Johnson, A. A. Peterson, C. F. Gelin, X. Deng, C. A. Dvorak, N. I. Carruthers, B. Lord, I. Fraser, L. Aluisio, K. J. Coe, B. Scott, T. Koudriakova, F. Schoetens, K. Sepassi, D. J. Gallacher, A. Bhattacharya and M. A. Letavic, *J. Med. Chem.*, 2018, **61**, 207; (*c*) C. Allais and W. R. Roush, *Org. Lett.*, 2017, **19**, 2646; (*d*) R. Watanabe, H. Mizoguchi, H. Oikawa, H. Ohashi, K. Watashi and H. Oguri, *Bioorg. Med. Chem.*, 2017, **25**, 2851; (*e*) R. Aeluri, R. J. Ganji, A. K. Marapaka, V. Pillalamarri, M. Alla and A. Addlagatta, *Eur. J. Med. Chem.*, 2015, **106**, 26; (*f*) T. Mesganaw and J. A. Ellman, *Org. Process Res. Dev.*, 2014, **18**, 1097; (*g*) N. N. Mateeva, L. L. Winfield and K. K. Redda, *Curr. Med. Chem.*, 2005, **12**, 551.

9 S. B. D. Jarvis and A. B. Charette, *Org. Lett.*, 2011, **13**, 3830.

10 *ClinCalc: Clinical Tools and Calculators for Medical Professionals*, http://clincalc.com/DrugStats/Top200Drugs.aspx, Oct 16, 2018.

11 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.

12 (*a*) A. Akin, M. T. Barrila, T. A. Brandt, A. M. R. Dechert-Schmitt, P. Dube, D. D. Ford, A. S. Kamlet, C. Limberakis, A. Pearsall, D. W. Piotrowski, B. Quinn, S. Rothstein, J. Salan, L. Wei and J. Xiao, *Org. Process Res. Dev.*, 2017, **21**, 1990; (*b*) P. Jones, S. Altamura, J. Boueres, F. Ferrigno, M. Fonsi, C. Giomini, S. Lamartina, E. Monteagudo, J. M. Ontoria, M. V. Orsale, M. C. Palumbi, S. Pesci, R. G. Roscilli, R. Scarpelli, C. Schultz-Fademrecht, C. Toniatti and M. Rowley, *J. Med. Chem.*, 2009, **52**, 7170; (*c*) J. Feng, Z. Zhang, M. B. Wallace, J. A. Stafford, S. M. Kaldor, D. B. Kassel, M. Navre, L. Shi, R. J. Skene, T. Asakawa, K. Takeuchi, R. Xu, D. R. Webb and S. L. Gwaltney, *J. Med. Chem.*, 2007, **50**, 2297; (*d*) J. G. Varnes, D. S. Gardner, J. B. Santella, J. V. Duncia, M. Estrella, P. S. Watson, C. M. Clark, S. S. Ko, P. Welch, M. Covington, N. Stowell, E. Wadman, P. Davies, K. Solomon, R. C. Newton, G. L. Trainor, C. P. Decicco and D. A. Wacker, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1645; (*e*) J. Cossy, C. Dumas and D. M. Pardo, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1343; (*f*) E. N. Petersen, E. Bechgaard, R. J. Sortwell and L. Wetterberg, *Eur. J. Pharmacol.*, 1978, **52**, 115.

13 For selected examples of synthesis of 3-substituted THPs *via* cycloadditions, see: ref. 1*f* and (*a*) Z. Wang, H. Xu, Q. Su, P. Hu, P. L. Shao, Y. He and Y. Lu, *Org. Lett.*, 2017, **19**, 3111; (*b*) H. Wang, W. Zhou, M. Tao, A. Hu and J. Zhang, *Org. Lett.*, 2017, **19**, 1710; (*c*) S. Yang, K. H. Rui, X. Y. Tang, Q. Xu and M. Shi, *J. Am. Chem. Soc.*, 2017, **139**, 5957*Via* intramolecular coupling, see: (*d*) L. Hou, Y. Yuan and X. Tong, *Org. Biomol. Chem.*, 2017, **15**, 4803. *Via* aziridinium ring expention, see: ref. 11.

14 (*a*) P. Schäfer, T. Palacin, M. Sidera and S. P. Fletcher, *Nat. Commun.*, 2017, **8**, 15762; (*b*) K. Kubota, Y. Watanabe, K. Hayama and H. Ito, *J. Am. Chem. Soc.*, 2016, **138**, 4338; (*c*) Y. Uozumi, *Pure Appl. Chem.*, 2007, **79**, 1481; (*d*) D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael and M. R. Gagne, *J. Am. Chem. Soc.*, 2000, **122**, 7905.

15 (*a*) K. Shibatomi, T. Okimi, Y. Abe, A. Narayama, N. Nakamura and S. Iwasa, *Beilstein J. Org. Chem.*, 2014, **10**, 323; (*b*) W. Chung, J. S. Carlson and C. D. Vanderwal, *J. Org. Chem.*, 2014, **79**, 2226.

16 T. Nishimine, K. Fukushi, N. Shibata, H. Taira, E. Tokunaga, A. Yamano, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2014, **53**, 517.

17 For full details and supporting references see ESI.†

18 M. H. Katcher and A. G. Doyle, *J. Am. Chem. Soc.*, 2010, **132**, 17402.

19 (*a*) M. E. Wood, S. Bissiriou, C. Lowe, A. M. Norrish, K. Senechal, K. M. Windeatt, S. J. Coles and M. B. Hursthous, *Org. Biomol. Chem.*, 2010, **8**, 4653; (*b*) J. Clayden, J. H. Pink, N. Westlund and F. X. Wilson, *Tetrahedron Lett.*, 1998, **39**, 8377; (*c*) D. Hoppe, M. Paetow and F. Hintze, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 394.

20 Deuterium erosion in the chlorination step, may be due to proto de-deuteration under acidic conditions and/or

relocation of D by S_N2' transformations. However, the latter pathway likely contributes only at minute levels as D atoms at C3 position of **rac-1-d** could only be detected by sensitive ^{2}H-NMR spectrscopic analyses. See ESI.†

21 (*a*) K. N. Houk, M. N. Paddon-Row and N. G. Rondan, *J. Mol. Struct.*, 1983, **103**, 197; (*b*) R. M. Magid and O. S. Fruchey, *J. Am. Chem. Soc.*, 1977, 8368.

22 B. L. Kormos and C. J. Cramer, *J. Org. Chem.*, 2003, **68**, 6375.

23 (*a*) J. B. Langlois, D. Emery, J. Mareda and A. Alexakis, *Chem. Sci.*, 2012, **3**, 1062; (*b*) A. Alexakis, J. E. Backvall, N. Krause, O. Pamies and M. Dieguez, *Chem. Rev.*, 2008, **108**, 2796.

24 For use of these molecules in elucidating the mechanism of Rh-catalyzed asymmetric additions see: L. Dijk, R. Ardkhean, M. Sidera, S. Karabiyikoglu, O. Sari, T. D. W. Claridge, R. Paton and S. P. Fletcher, *ChemRxiv*, 2019, DOI: 10.26434/chemrxiv.8208617.v1.

