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Asymmetric Catalysis

Dynamic Kinetic Resolution Allows Control of Remote Stereochemistry in Asymmetric Hydrogen Borrowing Alkylation

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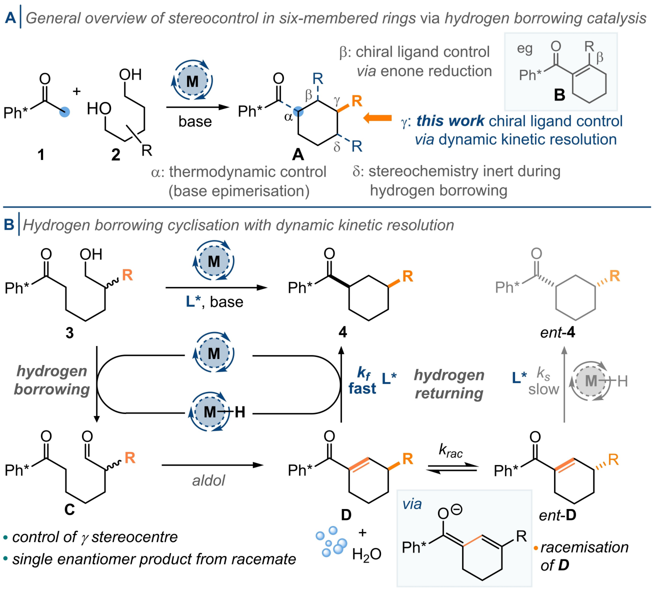
Abstract: A catalytic asymmetric method for the synthesis of γ-substituted ketones via hydrogen borrowing alkylation of both racemic linear precursors and 1,5-diols is described. The base mediated racemization of an intermediate cyclohexenone to facilitates a dynamic kinetic resolution, affording highly enantioenriched cyclohexanes in excellent yields, which could be further functionalized by removal of the Ph* group. DFT modelling revealed the mode of enantioinduction to be a stepwise process comprising of a hydride transfer and a coordination change to a π-allylic enolate complex with the iridium catalyst.

Hydrogen borrowing (HB) catalysis has recently emerged as a powerful method for C–C bond formation enabling use of alcohols as electrophiles via a temporary change in oxidation state.[1] Importantly, this negates the use of toxic alkyl halides and pseudo-halides. Despite large advances in the field, asymmetric HB methods are relatively underexplored (in particular for C–C bond formation) and would provide an opportunity to convert racemic alcohols into prochiral intermediates, such as enones, that can subsequently be reduced to give enantioenriched products.[2]

We have previously reported a HB-based annulation process using Ph* ketones and 1,5-diols to afford six-membered rings; these reactions form two new C–C bonds and their efficiency can be attributed to the acyl Ph* (C_6Me_5) group.[3] Here the unique ability of the two *ortho* methyl groups to protect the carbonyl prevents nucleophilic attack by metal hydrides or enolates in situ. Building upon our work to access racemic cyclohexanes we have shown that the absolute stereochemistry can be influenced at three of the four stereocentres by using various strategies (**A**, Scheme 1A). While distant (eg. δ) centres already present within the diol remain unchanged,[3a] stereochemical determination at the α-position is achieved using thermodynamic control via base mediated epimerisation in situ (**A**). However, most work in this field has concentrated on asymmetric induction at the β-position (**B**). In this case, reduction of an intermediate tetra-substituted enone by a catalyst/chiral ligand leads to control of absolute stereochemistry in the products.[4] An outstanding challenge lies in stereochemical control of the γ-stereogenic centre, which has been observed to be vulnerable to racemization under the basic conditions of the reaction.[3a,5]

However, we considered that this racemization could be used as an opportunity to conduct a dynamic kinetic



Scheme 1. A) General overview of stereocontrol during the hydrogen borrowing promoted formation of six-membered rings. B) This work: dynamic kinetic resolution. Ph* = C_6Me_5, **L*** = chiral ligand.

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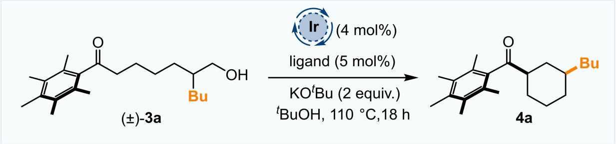
[+] Kirsten E. Christensen to whom correspondence regarding the X-ray structures should be addressed. Fernanda Duarte to whom correspondence regarding the DFT calculations should be addressed resolution (DKR) to obtain γ-functionalized enantioenriched ketones from racemic alcohol substrates. Here we were inspired by the elegant work of Zhao, and others, on the application of DKR processes to hydrogen borrowing reactions.[6] To explore the DKR step, we chose to investigate the hydrogen borrowing cyclisation of a racemic linear precursor alcohol, **3** (Scheme 1B). It was proposed that metal-catalyzed oxidation of **3** would give aldehyde **C**, which could undergo a base promoted aldol reaction to form enone **D**. This stereochemically labile intermediate could rapidly racemize through deprotonation/re-protonation via an extended enolate. In the presence of a chiral ligand, **L***, reduction of the matched enantiomer of enone **D** would afford the desired product **4**. The key to success would rely on balancing the rate of enone racemization versus reduction within a complex multistep reaction and would grant access to enantioenriched γ-substituted ketones from racemic alcohol starting materials.

We commenced our study with racemic alcohol substrate **3a**, and in line with our previous studies[4] in the presence of Ir(cod)acac (4 mol %), (*R*)-DTBM-SEGPHOS (**5**, 5 mol %) and KO^{t}Bu (2 equiv.) in ^{t}BuOH at 110 °C, the desired product **4a** was afforded in 84 % yield and 88:12 er (Table 1, entry 1). Comprehensive screening found that various chiral diphosphine ligands did not improve the enantioselectivity (see ESI for full details). When moving to the ferrocene ligand class, ligands such as **6** and **7** (entries 2–3) did not prove successful; however less commonly used ligand [R_P,S]-PPF-NH_2 (**8**) gave the desired product in 81 % yield and 97:3 er. Interestingly, two structural analogues **9** and **10** gave nearly racemic material (entries 5–6). In line with our original hypothesis, reducing the equivalents of base from 2.0 to 0.5 equivalents lowered the er from 97:3 to 69:31 (compare entries 4 and 7), presumably due to a reduction in the rate of racemization and the efficiency of the DKR. Increasing the base equivalents did not further increase the enantioselectivity and led to a decrease in yield (entry 8). Furthermore, we found that the reaction was highly sensitive to the nature of the base: KOH was detrimental to the reaction (entry 9) and changing the counterion led to inferior results (entry 10).

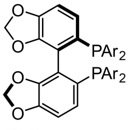
Using the optimized conditions (Table 1, entry 4), we examined the hydrogen borrowing cyclisation of a range of racemic starting materials (**3a–h**), all of which have functionality at the γ-position of the product (Scheme 2). Pleasingly, each example gave the combination of high yield and enantioselectivity in products **4a–h** which is indicative of a DKR process. In general, ligand **8** performed extremely well giving enantiomeric ratios of up to 98:2 combined with high yields of the products, enabling us to rule out a kinetic resolution pathway. Broadly, we found that (*R*)-DTBM-SEGPHOS ligand **5** was a second choice compared to ligand **8** (see Table 1) with one exception being the formation of compound **4h**, where a higher er was found using ligand **5**.

Table 1: Optimization of an enantioselective DKR hydrogen borrowing reaction.

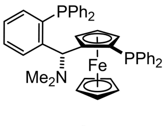


Entry	Base (equiv.)	Ligand	Yield[a]	dr[b]	er[c]
1	KO^{t}Bu (2.0)	**5**	87 (84)	91:9	12:88
2	KO^{t}Bu (2.0)	**6**	33	93:7	50:50
3	KO^{t}Bu (2.0)	**7**	87	90:10	52:48
4	**KO^{t}Bu (2.0)**	**8**	**82 (81)**	**91:9**	**97:3**
5	KO^{t}Bu (2.0)	**9**	14	92:8	46:54
6	KO^{t}Bu (2.0)	**10**	14	93:7	63:37
7	KO^{t}Bu (0.5)	**8**	39	90:10	69:31
8	KO^{t}Bu (4.0)	**8**	59	88:12	97:3
9	KOH (2.0)	**8**	51	92:8	67:33
10	NaO^{t}Bu (2.0)	**8**	35	92:8	78:22

Reaction conditions: Ir(cod)acac (4 mol%), ligand (5 mol%) and base in ^{t}BuOH (0.6 M) at 110 °C. [a] Determined by reverse phase HPLC analysis *vs* 1-bromo-2,3,4,5,6-pentamethylbenzene as an internal standard; values in parentheses indicate the yield of isolated product. [b] Determined by reverse phase HPLC analysis. [c] Determined by normal phase HPLC analysis using a chiral stationary phase. cod = 1,5-cyclooctadiene; acac = acetylacetonate; DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl; PPF = phenyl phosphino ferrocenyl



(R)-**5**: Ar = DTBM



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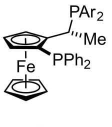

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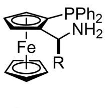
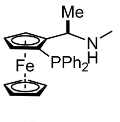
Ar = 3,5-Me$_2$-C$_6$H$_3$



8: R= Me
9: R= Ph



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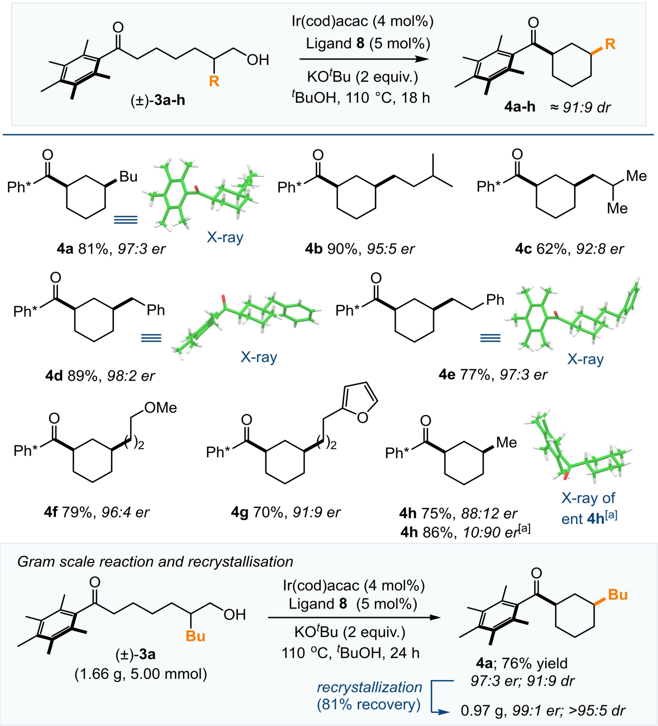
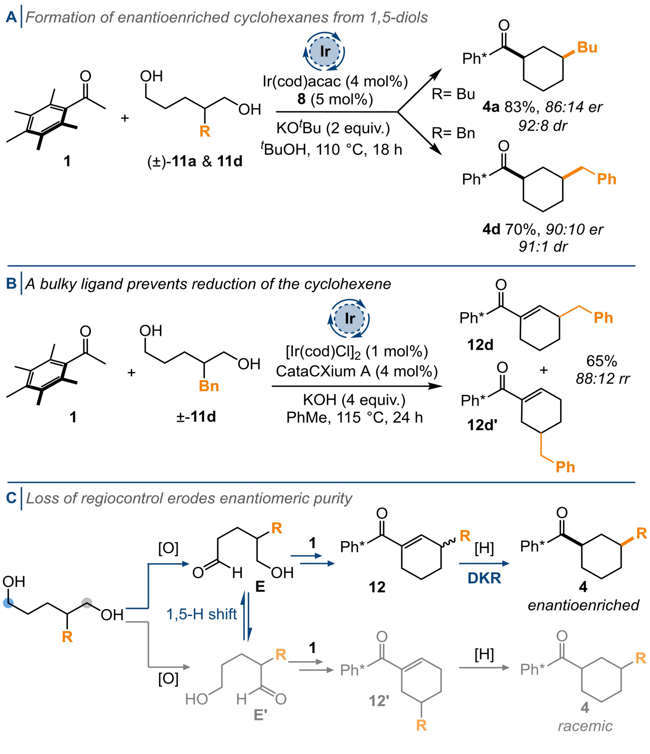


Scheme 2. Substrate scope of the dynamic kinetic resolution via hydrogen borrowing cyclisation. Yields shown are isolated material. Enantiomeric ratio (er) determined by HPLC analysis using a chiral stationary phase. [a] X-ray structure was obtained on material derived from a reaction utilizing (*R*)-**5**.

The Ph* group usually imparts crystallinity onto most compounds, allowing us to obtain single crystal X-Ray structures of products **4a**, **4d**, **4e** and **4h** allowing determination of their absolute stereochemistry (the remaining products are assigned by analogy).[7] It also provides an opportunity for a stereoselective recrystallization to enrich the enantiopurity of the compounds. This possibility was exemplified in a scale-up of the procedure (1.66 g, 5.00 mmol) whereby the er of product **4a** increased to 99:1 on recrystallisation, and approximately one gram of enantiopure product was obtained (Scheme 2).

Next we attempted to incorporate our strategy into the direct formation of a cyclohexane from a 1,5-diol and Ph*COMe **1** (Scheme 3A). The reaction furnished the target cyclohexanes **4** in a single step in good yields; however there was a decrease in the er compared to the analogous products in Scheme 2. To investigate this drop in selectivity, the key cyclohexene intermediate **D** (Scheme 1), was isolated by modifying the reaction system with a sterically hindered ligand (Scheme 3B).[8] In this reaction, the cyclohexene product **12** was formed as an 88:12 mixture of regioisomers (**12d**:**12d'**). We propose that this mixture is the key to understanding the drop in er for the formation of products **4a** and **4d** when using diols **11a** and **11d** (Scheme 3A) in comparison to starting from **3a** and **3d** (Scheme 2).

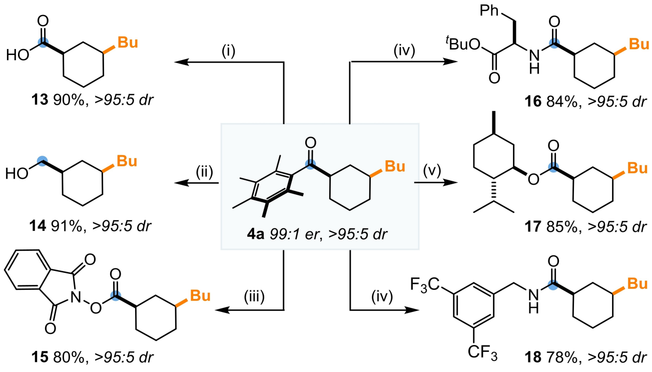
If we assume that a mixture of regiomeric enone intermediates is formed under the conditions in Scheme 3A, (here no enone was isolated and full reduction of the intermediates is assumed), only regioisomer **12d** is capable of undergoing the desired DKR process and give the enantioenriched product. Regioisomer **12d'** is not able to racemize at the γ-stereogenic centre and would be unproductive in the DKR. Note that this intermediate should still afford the reduced product (as a racemate) thereby lowering the overall er of the product but not affecting the reaction yield. Our proposition for the formation of two regioisomers in Scheme 3B has its origins in the formation of regiomeric hydroxy aldehydes **E** & **E'** derived from either (i) oxidation of alternate ends of the diol or (ii) interconversion of the aldehydes **E** & **E'** via a 1,5-hydride shift (Scheme 3C).[9] When **E/E'** undergo a dehydrating aldol reaction with **1**, they would lead inexorably to the formation of cyclohexenes **12** and **12'** respectively (this sequence involves an intermolecular aldol reaction, a 1,5-hydride shift and finally an intramolecular aldol reaction). Therefore, to obtain the highest possible enantioselective control and avoid regiomeric mixtures of the cyclohexene intermediate, the use of linear precursors is necessary. However, synthetic access to γ-substituted cyclohexanes is still possible from 1,5-diols with good enantioselectivity.



Scheme 3. A) Formation of enantioenriched cyclohexenes from 1,5-diols. B) Isolation of the key cyclohexene intermediate using a bulky phosphine ligand. C) Mechanism to rationalize the stereochemistry observed from 1,5-diols.

Finally, using **4a** produced on larger scale as a single enantiomer we were able to derivatise the Ph* ketone to a variety of functional groups (Scheme 4). Removal of the Ph* group with the addition of bromine, followed by direct addition of a nucleophile to the intermediate acid bromide formed a wide range of carbonyl derivatives in excellent yields and without loss in stereochemical integrity. We were able to form carboxylic acids **13**, alcohols **14**, esters **15** & **17**, and amides **16** & **18** in a one-pot procedure. As expected, the use of enantiopure nucleophiles gave compounds **16** and **17** as single diastereoisomers.

Intrigued by the efficacy of underutilized ligand **8**,[10] we investigated potential reaction pathways computationally. Density-functional theory (DFT) calculations were performed to model hydride transfer from the chiral iridium hydride bearing ligand **8** to the η^2-coordinated enone intermediate **12** with R=Bu (see ESI for analogous calculations with R=Me), in order to rationalise the observed



Scheme 4. Derivatization of the Ph* group. Br$_2$ (2 equiv.) CH$_2$Cl$_2$, −17 °C then add (i) aq. NaHCO$_3$; (ii) LiAlH$_4$ (5 equiv.); (iii) *N*-hydroxy phthalimide (2 equiv.), ^{i}Pr$_2$NEt (4 equiv.); (iv) H-D-Phe-O^{t}Bu·HCl (2 equiv.), ^{i}Pr$_2$NEt (4 equiv.); (v) L-(−)-menthol (2 equiv.); (vi) 3,5-ditrifluoromethyl benzylamine (2 equiv.).

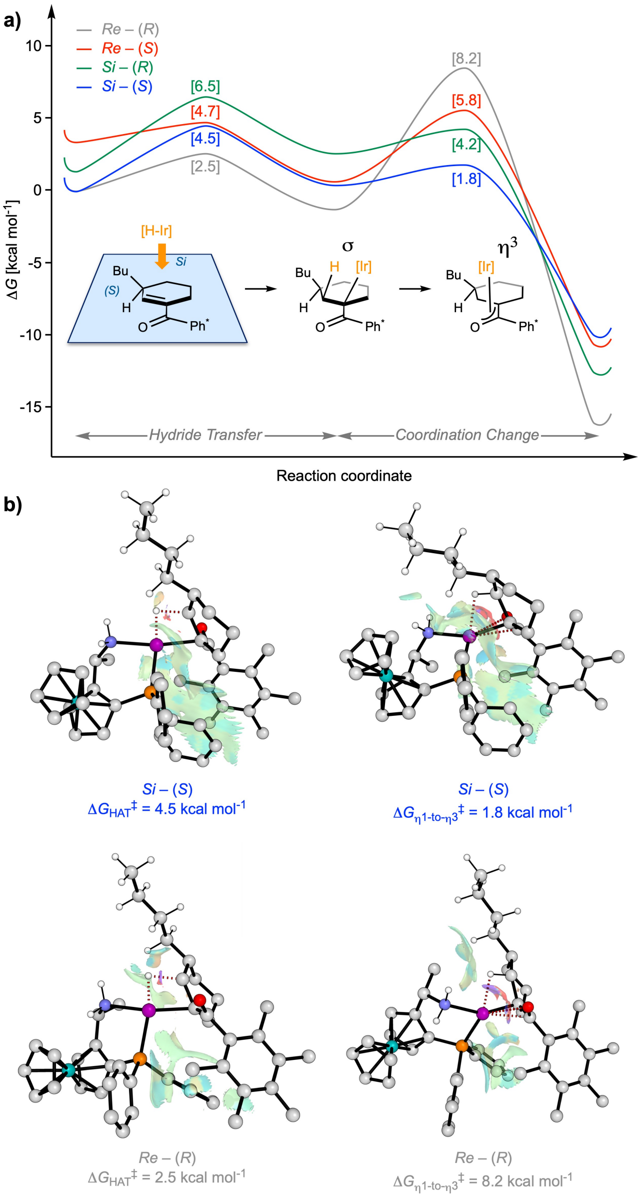


Figure 1. a) Energy profile for the two-step reaction involving hydride transfer from Ir-H to the enone and η^1-to- η^3 coordination change; relative energies in kcal mol^{-1} (shown in brackets) relative to the lowest-energy reactant complex, *Re*-(*R*). b) Non-covalent interaction (NCI) plots for the *Si*-(*S*) and *Re*-(*R*) transition states, where *Re* or *Si* indicate the enone face that Ir is coordinated to, and (*R*) or (*S*) refer to the enone isomer. Ir, Fe, C, N, O, P and H are shown in purple, light green, gray, blue, red, orange and white, respectively. C–H hydrogens except for the migrating hydride and those of the R=Bu group are omitted for clarity. Blue, red and green isosurface regions indicate strongly attractive, weakly attractive and repulsive NCIs, respectively, plotted with isovalue 0.3 in the range [−5,5].

selectivities. The Cambridge Crystallography Database contains the structure of a closely related Ir(I) complex with ligand **8**, which reveals a square planar geometry with a bidentate ligand binding mode.[11] Considering this, we constructed an initial catalyst-complex structure resembling the previously reported square planar geometry.

When considering the stereochemistry of the reaction, there are eight distinct configurations for the hydride transfer. However, only four of them, with the phosphine group *trans* to Ir-H, are reactive.[12] These four reactive configurations involve Ir coordinated to either the *Re*- or *Si*-face of the enone, which can be present as either the (*R*)- or the (*S*)-isomer (ESI, Figure SX1). These four reactive configurations were subjected to further calculations at the ωB97X-D3BJ/def2-QZVP/CPCM(*t*BuOH) level using the ORCA 5.0.3 program[13] (see ESI). Our calculations reveal a stepwise mechanism, in which the hydride first migrates from Ir to the carbon β to the carbonyl group, forming a σ-like complex where Ir is coordinated to the α-carbon. This complex then undergoes a coordination change from η^1 to η^3, resulting in a π-allylic enolate complex with Ir (Figure 1a). A difference in rate-limiting (and enantiodetermining) step was observed depending on the complex configuration. In the first step, the two configurations with the Bu group on the same face as the transferred hydride (*Re*-(*R*) and *Si*-(*S*)) exhibit the lowest barrier (Figure 1a, blue and gray profiles), while in the second step, the two *Si*-face configurations are preferred (Figure 1a, green and blue profiles).

The *Si*-(*S*) and *Re*-(*R*) configurations (Figure 1b, top and bottom, respectively) represent the lowest-energy pathway for the (*S*) product and the highest-energy pathway for the (*R*) product, respectively. A non-covalent interaction (NCI) analysis[14] for these pathways revealed favourable interactions between the Bu group and the Ir-complex in the hydride transfer for both configurations (Figure 1b, top left and bottom left), which are absent in the *Re*-(*S*) and *Si*-(*R*) pathways (see ESI). However, *Re*-(*R*) exhibits a high-energy transition state in the coordination change step with a late transition state (this makes the hydride transfer reversible) and it is the least favoured pathway amongst the four configurations, with Ir-α-C and Ir-O distances 0.16 and 0.17 Å shorter than in the *Si*-(*S*) transition state, respectively. In contrast, aromatic π-stacking interactions between the aryl phosphine Ph ring and the enolate Ph* stabilise both the *Si*-(*R*) and *Si*-(*S*) coordination change transition states, with the latter being the preferred pathway (Figure 1b, top right).

Using the Boltzmann average of the rate-determining barriers for the four different paths led to a computed er of 94:6 (**4a**) (and 89:11 for **4h**, R=Me, see ESI), in agreement with the experimentally determined values (97:3 er (**4a**) and 88:12 er (**4h**)). It is interesting (and beneficial) that with R = Bu, the two lowest energy pathways (*Si*-(*S*) and *Re*-(*S*)) both reduce the (*S*) enantiomer of the enone and, in this case, give the same product.

In conclusion, we have developed a hydrogen borrowing alkylation which enables stereochemical control of remote γ-stereocentres in substituted cyclohexanes using a dynamic kinetic resolution strategy. By utilising in situ racemization of a key enone intermediate, combined with a chiral iridium catalyst (Ir(cod)acac and [R_P,*S*]-PPF-NH$_2$), this DKR process affords enantioenriched carbocyclic products in high yields with excellent diastero- and enantiomeric control from racemic starting materials. These products could also be accessed directly from 1,5-diols, and the underlying stereochemical control for these substrates was investigated. The origins of the enantioselectivity were probed through DFT modelling, which described the energy barriers for a stepwise reaction mechanism comprising a hydride transfer and a coordination change to a π-allyl enolate complex with the catalyst. Finally, derivatisation of the Ph* ketone demonstrates the utility of this strategy for accessing a diverse range of products with defined stereochemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: hydrogen borrowing · dynamic kinetic resolution · cyclohexanes · asymmetric synthesis · iridium

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[1] a) J. M. Ketcham, I. Shin, T. P. Montgomery, M. J. Krische, *Angew. Chem. Int. Ed.* **2014**, *126*, 9294; b) H. Aitchison, R. L. Wingad, D. F. Wass, *ACS Catal.* **2016**, *6*, 7125; c) M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026; d) B. G. Reed-Berendt, K. Polidano, L. C. Morrill, *Org. Biomol. Chem.* **2019**, *17*, 1595; e) B. G. Reed-Berendt, D. E. Latham, M. B. Dambatta, L. C. Morrill, *ACS Cent. Sci.* **2021**, *7*, 570–585.

[2] For reviews see, a) T. Kwok, O. Hoff, R. J. Armstrong, T. J. Donohoe, *Chem. Eur. J.* **2020**, *26*, 12912; b) A. Alexandridis, A. Quintard, *ChemCatChem.* **2024**, *16*, e202400902; c) Y. Gao, G. Hong, B.-M. Yang, Y. Zhao, *Chem. Soc. Rev.* **2023**, *52*, 5541; See also, d) M. Y. Jin, Y. Zhou, D. Xiao, Y. You, Q. Zhen, G. Tao, P. Yu, X. Xing, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112993.

[3] a) W. M. Akhtar, R. J. Armstrong, J. R. Frost, N. G. Stevenson, T. J. Donohoe, *J. Am. Chem. Soc.* **2018**, *140*, 11916–11920; b) R. J. Armstrong, W. M. Akhtar, J. R. Frost, K. E. Christensen, N. G. Stevenson, T. J. Donohoe, *Tetrahedron* **2019**, *75*, 130680; c) A. Kaithal, L.-L. Gracia, C. Camp, E. A. Quadrelli, W. Leitner, *J. Am. Chem. Soc.* **2019**, *141*, 17487–17492; d) A. Jana, K. Das, A. Kundu, P. R. Thorve, D. Adhikari, B. Maji, *ACS Catal.* **2020**, *10*, 2615–2626; e) L. Bettoni, S. Gaillard, J.-L. Renaud, *Chem. Commun.* **2020**, *56*, 12909–12912.

[4] a) R. J. Armstrong, W. M. Akhtar, T. A. Young, F. Duarte, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2019**, *58*, 12558–12562; see also, b) D. M. J. Cheang, R. J. Armstrong, W. M. Akhtar, T. J. Donohoe, *Chem. Commun.* **2020**, *56*, 3543–3546.

[5] As a complementary approach we have recently shown that the hydrogen borrowing alkylation of Ph*COMe **1** with enantiopure 1,2-aminoalcohols could proceed with *retention* of configuration at the γ-position relative to the carbonyl group. In this scenario, the conditions were modified to reduce the loading of base, and the aminoalcohol substrates were appended with a bulky Tr protecting group on nitrogen. These factors combined to suppress the normally observed racemization of the sensitive aldehyde and enone intermediates, see: a) C. J. J. Hall, W. R. F. Goundry, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2021**, *60*, 6981–6985.

[6] For a review of DKR see; a) F. F. Huerta, A. B. E. Minidis, J. E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321–331; b) V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528–4561; see also; c) Z. Q. Rong, Y. Zhang, R. H. B. Chua, H. J. Pan, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 4944–4947; d) A. Quintard, J. Rodriguez, *Chem. Commun.* **2016**, *52*, 10456–10473; e) L. C. Yang, Y. N. Wang, Y. Zhang, Y. Zhao, *ACS Catal.* **2017**, *7*, 93–97; f) J. Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 465–469; g) Z. Q. Rong, Z. Yu, C. Weng, L. C. Yang, S. Lu, Y. Lan, Y. Zhao, *ACS Catal.* **2020**, *10*, 9464–9475; h) X. Zhang, W. Ma, J. Zhang, W. Tang, D. Xue, J. Xiao, H. Sun, C. Wang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202203244; i) B. Lainer, S. Li, F. Mammadova, P. Dydio, *Angew. Chem. Int. Ed.* **2024**, *63*, e202408418.

[7] Single crystal X-ray diffraction data were collected using a (Rigaku) Oxford Diffraction SuperNova diffractometer. Structures were solved using "Superflip" [L. Palatinus, G. Chapuis, *J. Appl. Cryst.* **2007**, *40*, 786.] before refinement with CRYSTALS a) P. Parois, R. I. Cooper, A. L. Thompson, *Chem. Cent. J.* **2015**, *9*, 30; b) R. I. Cooper, A. L. Thompson, D. J. Watkin, *J. Appl. Crystallogr.* **2010**, *43*, 1100] as per the Supporting Information (CIF). Deposition numbers 2393531 (for **4a**), 2393532 (for **4d**), 2393533 (for **4e**), 2393534 (for **4h**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallo-graphic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[8] a) L. B. Smith, R. J. Armstrong, D. Matheau-Raven, T. J. Donohoe, *J. Am. Chem. Soc.* **2020**, *142*, 2514–2523; b) D. Shen, D. L. Poole, C. C. Shotton, A. F. Kornahrens, M. P. Healy, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2015**, *54*, 1642–1645.

[9] L. B. Smith, R. J. Armstrong, J. Hou, E. Smith, M. Sze, A. J. Sterling, A. Smith, F. Duarte, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2023**, *62*, e202307424.

[10] a) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735–740; b) W. Zeng, G. Y. Chen, Y. G. Zhou, Y. X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750–751.

[11] F. Camponovo, *Chiral Ferrocenyl Amidines as modular ligands for Applications in Asymmetric Catalysis, Dissertation*, ETH Zurich, **2009**; 10.3929/ethz-a-005772740. See also CCDC 720942.

[12] In the other four cases, the amine moiety has a much lower *trans* effect, thus preventing the Ir-H bond from breaking (see ESI).

[13] a) J.-D. Chai, M. Head-Gordon, *J. Chem. Phys.* **2008**, *128*, 084106; b) A. Najibi, L. Goerigk, *J. Chem. Theory Comput.* **2018**, *14*, 5725–5738; c) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297; d) F. Neese, F. Wennmohs, U. Becker, C. Riplinger, *J. Chem. Phys.* **2020**, *152*, 224108.

[14] R. A. Boto, F. Peccati, R. Laplaza, C. Quan, A. Carbone, J.-P. Piquemal, Y. Maday, J. Contreras-García, *J. Chem. Theory Comput.* **2020**, *16*, 4150–4158.

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