



HAL
open science

A Merger of Relay Catalysis with Dynamic Kinetic Resolution Enables Enantioselective β -C(sp³)-H Arylation of Alcohols

Bruno Lainer, Shuailong Li, Flora Mammadova, Pawel Dydio

► **To cite this version:**

Bruno Lainer, Shuailong Li, Flora Mammadova, Pawel Dydio. A Merger of Relay Catalysis with Dynamic Kinetic Resolution Enables Enantioselective β -C(sp³)-H Arylation of Alcohols. *Angewandte Chemie International Edition*, 2024, 63 (35), pp.e202408418. 10.1002/anie.202408418 . hal-04897921

HAL Id: hal-04897921

<https://hal.science/hal-04897921v1>

Submitted on 20 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



Dual Catalysis Hot Paper

 How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202408418
 doi.org/10.1002/anie.202408418

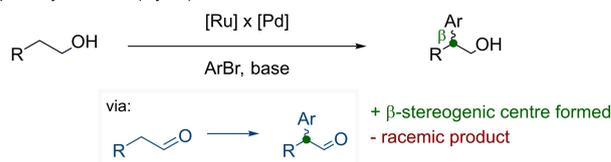
A Merger of Relay Catalysis with Dynamic Kinetic Resolution Enables Enantioselective β -C(sp³)-H Arylation of Alcohols

 Bruno Lainer⁺, Shuailong Li⁺, Flora Mammadova⁺, and Paweł Dydio*

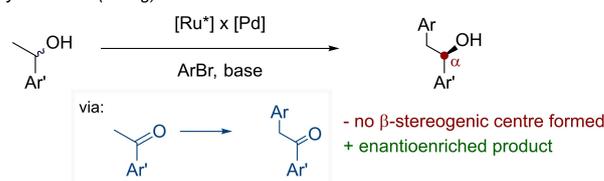
Abstract: The conceptual merger of relay catalysis with dynamic kinetic resolution strategy is reported to enable regio- and enantioselective C(sp³)-H bond arylation of aliphatic alcohols, forming enantioenriched β -aryl alcohols typically with >90:10 enantiomeric ratios (up to 98:2 er) and 36–74% yields. The starting materials bearing neighbouring stereogenic centres can be converted to either diastereomer of the β -aryl alcohol products, with >85:15 diastereomeric ratios determined by the catalysts. The reactions occur under mild conditions, ensuring broad compatibility, and involve readily available aryl bromides, an inorganic base, and commercial Ru- and Pd-complexes. Mechanistic experiments support the envisioned mechanism of the transformation occurring through a network of regio- and stereoselective processes operated by a coherent Ru/Pd-dual catalytic system.

Relay catalysis can unlock otherwise challenging transformations,^[1] including formal C(sp³)-C(sp³) bond metathesis,^[2] depolymerisation of polyethylene,^[3] or difficult cross-coupling and functionalisation reactions.^[4] In that context, we have developed a Ru-/Pd-dual relay for challenging regioselective arylation of primary aliphatic alcohols at unactivated β -C(sp³)-H bonds, occurring through transient more reactive aldehyde intermediates and forming β -aryl alcohol products as racemic mixtures (Figure 1a, top).^[5] In turn, Wang and co-workers have recently reported a Ru-/Pd-dual relay for entioconvergent β -arylation of racemic α -aryl-ethanols, occurring through transient aryl methyl ketones and forming enantioenriched α,β -bisaryl-ethanol products without a stereogenic centre at the β -position (Figure 1a, bottom).^[6] However, enantioselective β -

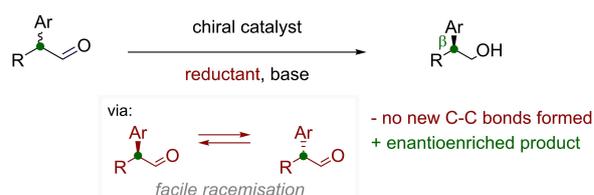
(a) β -Arylation of alcohols under relay catalysis
 - primary alcohols (Dydio)



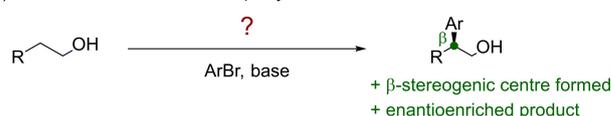
- α -aryl ethanols (Wang)



(b) Dynamic reductive kinetic resolution of racemic α -aryl aldehydes
 - Ru-catalyzed hydrogenation with H₂ (Zhou, List)
 - biocatalytic reduction with SsADH-10 (Berkowitz)



(c) **This work:** Enantioselective β -arylation of alcohols



Can relay catalysis be integrated with dynamic kinetic resolution for transient aldehyde intermediates to enable direct enantioselective β -arylation of alcohols?

Figure 1. Context & the current work.

arylation of alcohols remains unprecedented. In that case, the new stereogenic centre of the aldehyde (or ketone) intermediate, even if installed enantioselectively by a chiral Pd catalyst, undergoes facile racemisation under the reaction conditions^[7] resulting in the racemic product formation, thereby calling for a new strategy.

Dynamic kinetic resolution (DKR),^[8] which capitalises on the fast racemisation of starting materials, is a strategy that enables to convert racemic starting materials into enantioenriched products. In that context, Zhou^[9] and List^[10] reported hydrogenation of racemic α -aryl aldehydes with H₂ as a reducing reagent to form enantioenriched β -aryl

[*] S. Li,⁺ F. Mammadova,⁺ P. Dydio

University of Cambridge
 Lensfield Road, Cambridge, CB2 1EW, UK
 E-mail: pd552@cam.ac.uk

B. Lainer,⁺ S. Li,⁺ F. Mammadova,⁺ P. Dydio
 University of Strasbourg, CNRS
 ISIS UMR 7006
 8 Allée Gaspard Monge, 67000 Strasbourg, France

[⁺] These authors contributed equally to this work as the first author.

© 2024 The Authors. Angewandte Chemie International Edition published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

alcohols in the presence of chiral Ru complexes and a strong base (Figure 1b). In turn, Berkowitz reported a biocatalytic protocol for the same transformation using alcohol dehydrogenase isozyme 10 from *Sulfolobus solfataricus* (Figure 1b).^[11]

We hypothesised that a conceptual merger of relay catalysis with dynamic kinetic resolution of racemic transient aldehyde intermediates could enable direct enantioselective β -arylation of aliphatic alcohols (Figure 1c). The reaction design separates the formation of the new stereogenic centre by the Pd-catalyst from the control of its stereochemistry imposed by the Ru-catalyst. In essence, the latter can differentiate between two transient interconverting enantiomeric aryl aldehyde intermediates and selectively reduce one of them to the target enantiomer of the product.

At the outset of these studies, we considered the critical kinetic conditions that must be met to favour the selective formation of enantiomer (*R*)-**3** through the devised network of reactions starting from alcohol **1** and aryl bromide **2** (Scheme 1). First, alcohol **1** is reversibly oxidised to aldehyde **ald-1** by a hydrogen-borrowing Ru complex.^[12] Then, **ald-1** undergoes arylation with aryl bromide **2** by a Pd catalyst^[13] forming (*R*)-**ald-3** and (*S*)-**ald-3**, which are in a dynamic equilibrium facilitated by a base.^[7] Last, (*R*)-**ald-3** is selectively reduced to (*R*)-**3** by the same Ru complex. To fulfil the envisioned scenario, the reduction of (*R*)-**ald-3** must be significantly faster than that of (*S*)-**ald-3** (condition 1), and racemisation of (*S*)-**ald-3** must be faster than its reduction to alcohol (*S*)-**3** (condition 2), satisfying the principles of DKR of racemic **int-3**.^[8] In addition, reversible oxidation of target (*R*)-**3** must be slower than both oxidation of **1** (condition 3) and arylation of **ald-1** (condition 4), thereby preventing the erosion of enantioenrichment of (*R*)-**3**.^[14] Importantly, the selection of the catalysts and the

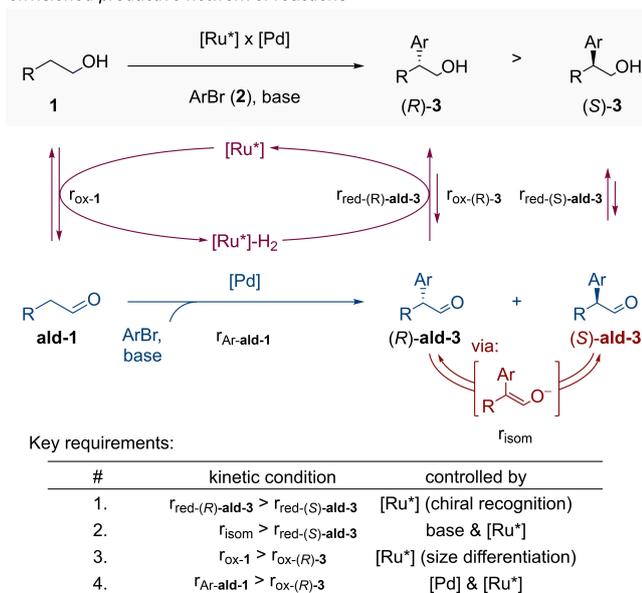
reaction conditions also needs to take into account plausible side processes (Figure S1).^[15]

Initial exploration of the devised relay for the β -arylation of primary alcohols with aryl bromides using Ru catalysts developed by Zhou^[9] and List^[10] for enantioselective hydrogenation of racemic α -aryl aldehydes with H₂ and Pd catalysts for aldehyde arylation^[13c-e] resulted in the formation of β -aryl alcohols with low levels of enantioenrichment (up to ~70:30 enantiomeric ratio, er, see below). Control experiments indicated that, while these Ru catalysts are highly enantioselective for hydrogenation of racemic α -aryl aldehydes with H₂ as a reducing reagent, they are poorly selective for transfer hydrogenation of racemic α -aryl aldehydes with alcohols as reducing reagent,^[16] that is, the reactivity required for the devised relay shown in Scheme 1.

Upon evaluation of a range of different Ru and Pd complexes and conditions, we found that the model reaction of **1a** (0.38 mmol) and **2a** (0.25 mmol) formed preferentially aryl alcohol (*R*)-**3aa** in 93:7 enantiomeric ratio (er) and 59% NMR yield (51% isolated yield), in the presence of (*S,S*)-**Ru*-1** (5 mol %), Pd₂dba₃*CHCl₃/rac-btfm-garphos (**L1**; 1.25 mol %/ 5 mol %), and Cs₂CO₃ (1 mmol) in 1,4-dioxane (2 mL) at 75°C for 16 h. Control experiments confirmed the importance of each element of the reaction conditions, as summarised in Figure 2. For instance, the replacement of **Ru*-1** with **Ru*-2**, previously employed in enantioconvergent β -arylation of racemic α -aryl-ethanols,^[6] resulted in the formation of nearly racemic **3aa** (48:52 er) in 68% yield (entry 3). In turn, the use of **Ru*-3** or **Ru*-4** reported by Zhou^[9] and List^[10] led to the formation of **3aa** in 51:49 to 71:29 er's and 15–89% yield (entries 4–5). Further, the use of **Ru*-5**, reported to be selective in many enantioselective hydrogen transfer reactions,^[16] led to the formation of **3aa** as a nearly racemic mixture, 45:55 er, in 78% yield (entry 6). In turn, when **L1** was replaced with dppf (**L2**), rac-binap (**L3**), *t*Bu₃P (**L4**), sphos (**L5**), or q-phos (**L6**), used previously in the arylation of alcohols^[5,6] or aldehydes,^[13c-e] the reactions occurred in substantially diminished yields (entry 7–11). Lastly, a type of the Pd precursor, the base, solvent, and temperature proved also essential for the enantioselectivity and yield of the reaction (entries 12–16). Noteworthy, the use of Pd₂dba₃ in place of Pd₂dba₃*CHCl₃, irrespective of the supplier, led to diminished reproducibility of the reaction outcome.^[17]

With the optimised conditions for the model reaction, we next investigated the performance of this cooperative reaction network with starting materials of different structures and electronic properties (Figure 3). We found that a range of *para*- and *meta*-substituted aryl bromides **2b–2k** bearing varied electron-withdrawing and electron-donating functional groups reacted effectively with isoamyl alcohol **1a**, forming enantioenriched alcohols **3ab–3ak** (89:11 to 96:4 er's, 35–65% yields). However, the reactions with *ortho*-substituted aryl bromides, such as **2l–2m**, were unproductive, presumably due to the increased steric hindrance. In turn, polycyclic aryl bromides, such as biphenyl **2n** and naphthyl **2o**, proved competent substrates in these reactions, forming **3an–3ao** in 90:10–93:7 er's and 48–56% yields. Finally, the reactions of **1a** with heteroaryl

envisioned productive network of reactions



Scheme 1. Reaction design merging relay catalysis with dynamic kinetic resolution of transient intermediates.

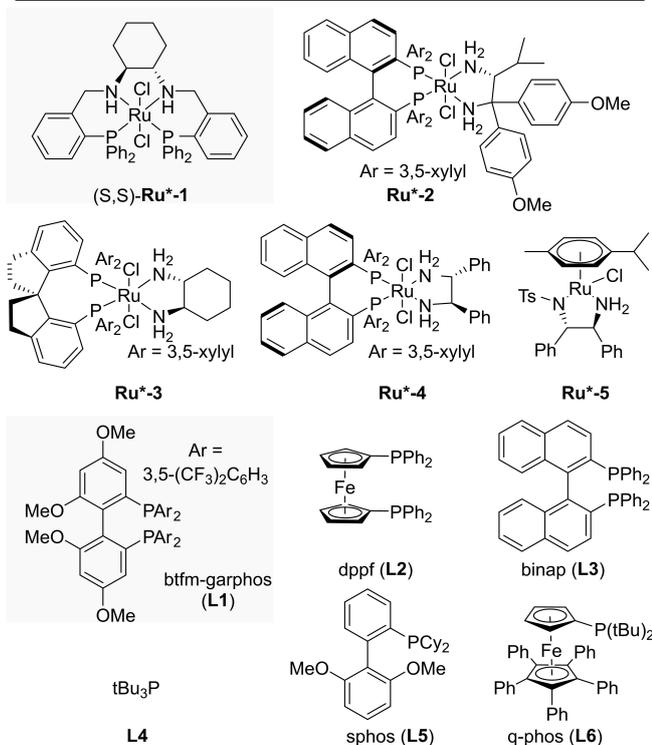
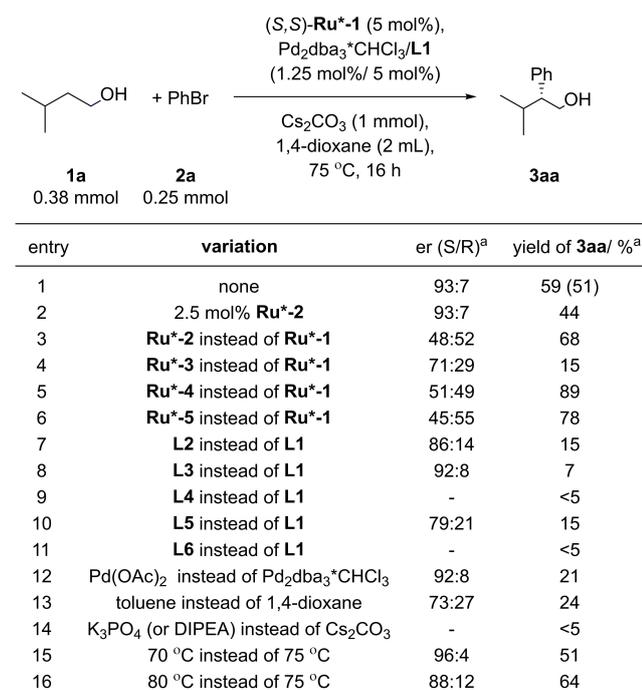


Figure 2. Reaction development. ^a Enantiomeric ratios (er's) were determined by supercritical fluid chromatography (SFC) with chiral stationary phase; spectroscopic yields determined by the ¹H NMR analysis with an internal standard; yield of isolated material reported in parentheses; the absolute configuration assigned based on the optical rotation.^[9]

bromides, such as benzothiophene **2p** and benzofuran **2q**, produced target **3ap–3aq** in 93:7–97:3 er's and 43–49 % yields, while the reactions with indoles **2r–2s** formed low amounts of the target products.

We also found that a range of structurally varied alcohols are effective substrates for the title reaction, with enantioenrichment of the product depending on the size of the γ -substituents of the starting material (Figure 3). Specifically, **1b–1f** bearing cyclohexyl, tetrahydropyran, piperidine, or cyclopentyl rings next to the reacting $\beta\text{-C}(\text{sp}^3)\text{-H}$ bond reacted with **2a** to form products **3ba–3fa** with enantioselectivity and yields, similar to those for the model reaction for alcohol **1a** bearing isopropyl group (84:16–95:5 er's and 54–70 % yields vs. 93:7 er and 59 % yield). In sharp contrast, the reaction for **1g** bearing a cyclopropyl ring, which is less bulky than isopropyl or any other rings,^[18] produced **3ga** with lower enantioselectivity (70:30 er, 60 % yield), similar to that of the product formed in the reaction for least bulky linear alcohol **1h**, forming **3ha** with 75:25 er's and 72 % yield. In line with the influence of γ -branching on the enantiocontrol, the reaction of **1i** containing large diphenylmethyl moiety with **2a** led to **3ia** with excellent enantioselectivity (98:2 er, 54 % yield), while the reaction of **1j** containing smaller benzyl group produced **3ja** with moderate selectivity (74:26 er, 71 % yield). Lastly, **1k** containing naphthyl ring and **1l** with *tert*-butyl group proved challenging starting materials; the former reacted to form **3ka** bearing β,β -bisaryl alcohol with modest stereoselectivity (61:39 er, 55 % yield), presumably due to the difficulty in differentiating between naphthyl and phenyl groups, while the latter formed only traces of **3la** (<5 %), most likely due to too large steric hindrance imposed by the bulky *tert*-butyl group.

Bolstered by these results, we studied the β -arylation of alcohols containing neighbouring stereogenic centres and their influence on the stereocontrol of the product (Figure 4). We found that in the case of β -citronellol **1m**, a natural acyclic monoterpene bearing a stereogenic centre in γ -site, (*S*)-**1m** and (*R*)-**1m** can be selectively converted to any of four possible stereoisomers by selecting the starting material and a suitable enantiomer of **Ru**^{*}-1 complex. Specifically, the reaction of (*R*)-**1m** and **2x** formed either **3mx** in 85:15 diastereomeric ratio (dr) and 74 % yield with (*R,R*)-**Ru**^{*}-1 or **3mx'** in 85:15 dr and 65 % yield with (*S,S*)-**Ru**^{*}-1. In turn, (*S*)-**1m** reacted with **2x**, forming either ent-**3mx** in 85:15 dr and 70 % yield with (*S,S*)-**Ru**^{*}-1 or ent-**3mx'** in 87:13 dr and 58 % yield with (*R,R*)-**Ru**^{*}-1. Similarly, dihydronopol **1n**, a bicyclic terpene derivative, reacted with **2e** to form either **3ne** or **3ne'** as the major diastereomer, depending on the chirality of **Ru**^{*}-1 (90:10 dr and 50 % yield or 86:14 dr and 40 % yield, using and (*R,R*)-**Ru**^{*}-1 or (*S,S*)-**Ru**^{*}-1, respectively). These examples showcase the ability of the method to construct chiral building blocks containing multiple stereogenic centres with precise stereocontrol over the new stereogenic centres by the catalysts used.

Finally, we performed a series of experiments in support of the envisioned mechanism of the transformation (Figure 5). Specifically, the model reaction of **1a** and **2b** in the presence of (*S,S*)-**Ru**^{*}-1 and Pd complex with enantiomerically pure either (*R*)-**L1** or (*S*)-**L1** resulted in the formation of the same (*R*)-**3aa** as the major enantiomer with comparable er's, while the replacement of (*S,S*)-**Ru**^{*}-1 with racemic

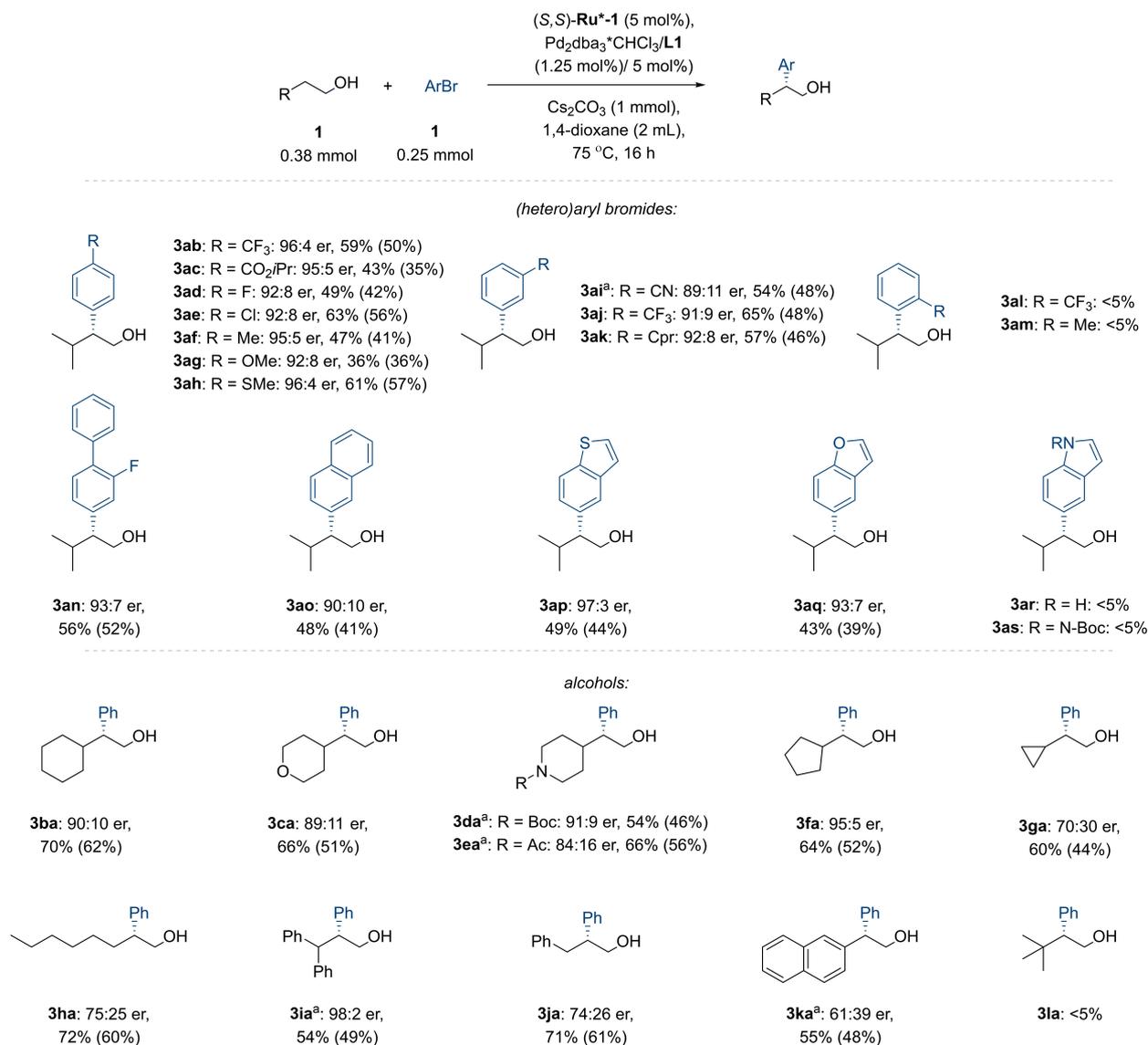
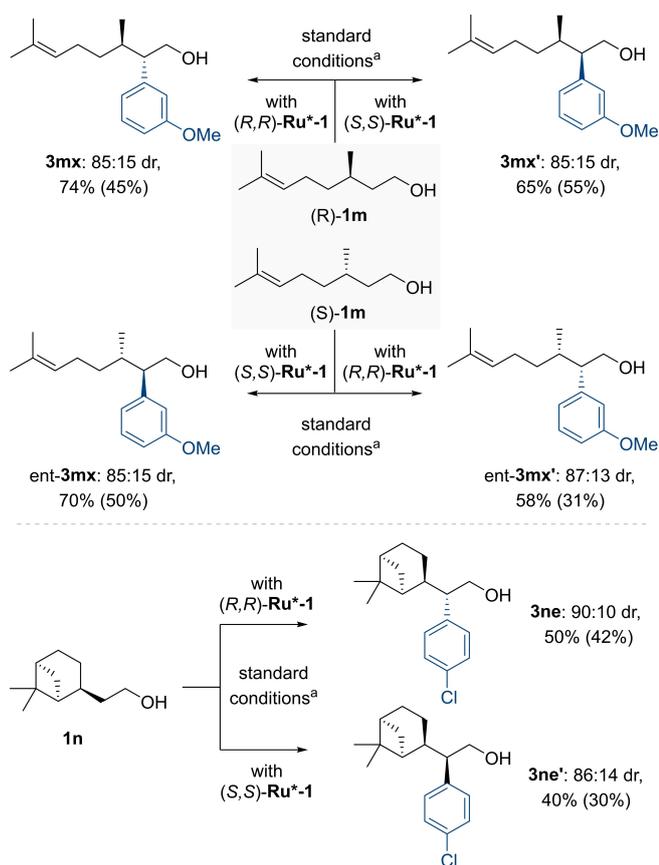


Figure 3. Scope of (hetero)aryl bromides and achiral alcohols. Enantiomeric ratios (er's) were determined by supercritical fluid chromatography (SFC) with chiral stationary phase; due to the volatility of some products, both spectroscopic and isolated yields (in parenthesis) are reported; the absolute configuration determined by x-ray crystallography, by comparison of the optical rotations with those reported in the literature,^[9,19] or assigned by analogy (see the SI).^a The opposite enantiomer of the product formed preferentially by using (*R,R*)-Ru^{*}-1 instead of (*S,S*)-Ru^{*}-1.

Ru^{*}-1 furnished nearly racemic products (Figure 5a). These data demonstrate that the chiral Ru complex primarily determines the stereochemistry of the product. In turn, the experiments with enantioenriched intermediate (*R*)-ald-3aa (83:17 er) added to the reaction of **1c** and **2a** under otherwise standard conditions resulted in the formation of either (*R*)-3aa or (*S*)-3aa, as the major enantiomer, depending on the presence of either (*S,S*)-Ru^{*}-1 or (*R,R*)-Ru^{*}-1 (Figure 5b). These results illustrate that the aryl aldehyde intermediates do readily racemise under reaction conditions, and one enantiomer is selectively reduced to the alcohol with stereochemistry determined by the chiral Ru complex. Moreover, the reaction of racemic ald-3aa and *n*-octanol (**1h**) as a hydrogen donor in the presence of (*S,S*)-Ru^{*}-1 and a base furnished enantioenriched (*R*)-3aa in 93:7 er and

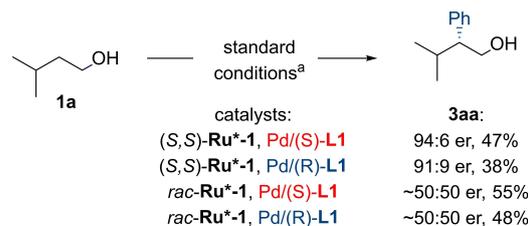
65% yield. The experiment illustrates that dynamic kinetic resolution by the Ru complex is independent of the Pd-catalyzed arylation (Figure 5c). Finally, when the model reaction was monitored over an extended period, we observed two distinct phases that can be attributed to the kinetic and thermodynamic regimes controlling the stereochemistry of the product (Figure 5d). In the productive phase, lasting ~24 h, we observed a steady formation of product **3aa** with a constant ~93:7 er (kinetic product). However, in the subsequent phase, starting > 24 h, when the formation of **3aa** was essentially completed, the enantioenrichment began to deteriorate toward the racemic mixture (thermodynamic product), in accordance with the DKR mechanism and the reversibility of the hydrogen borrowing processes. Altogether, the results of these experiments are



in line with the envisioned relay catalysis incorporating dynamic kinetic resolution of transient aldehyde intermediates to control the regio- and enantioselectivity of the overall transformation.

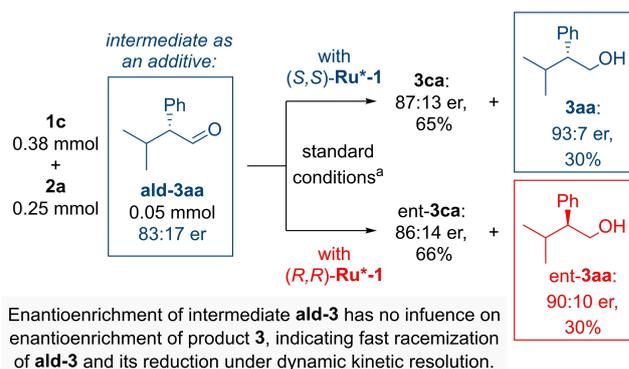
Overall, the work presented here introduces a new multicatalytic strategy for challenging regio- and stereoselective functionalisation of molecules at their otherwise unreactive positions. The method rests on the merger of hydrogen borrowing catalysis – temporarily activating starting materials, with C–H functionalisation catalysis – modifying activated intermediates, and dynamic kinetic resolution catalysis – controlling the stereochemistry of the products formed. The study illustrates the capacity of orchestrating the reactivities of multiple catalysts that mediate multiple parallel processes occurring under the same conditions. In a broader sense, the study reveals the potential of relay catalysis that seamlessly merges multiple catalytic processes connected through common intermediates into productive coherent systems.

a. Influence of stereochemistry of **Ru^{*}-1** and Pd/**L1** on the reaction

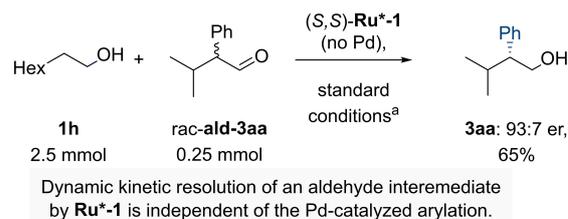


Stereochemistry of Pd/**L1** complex has nearly no influence on the enantioselectivity of the reaction.

b. Reduction of enantioenriched aldehyde interm. under the reaction conditions



c. Dynamic kinetic resolution under hydrogen transfer catalysis by (*S,S*)-**Ru^{*}-1**



d. Model reaction followed in time for an extended period

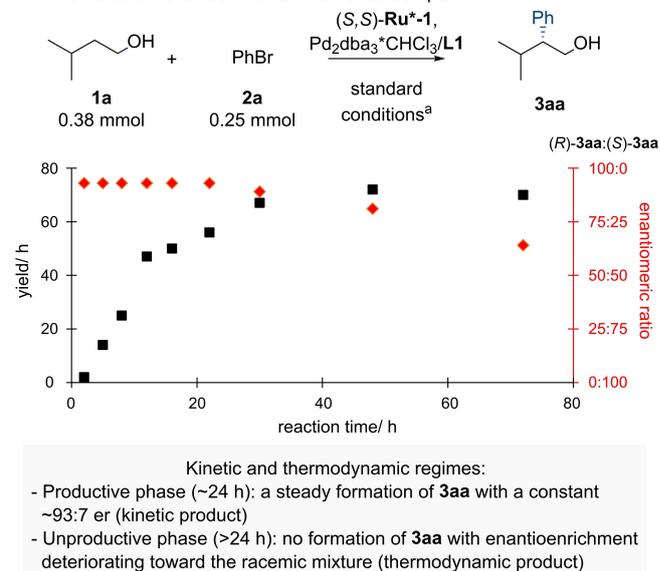


Figure 5. Mechanistic experiments. ^a Standard conditions are shown in Figure 3, racemic **L1** used, unless noted otherwise.

Acknowledgements

We acknowledge funding from the European Research Council (ERC-StG-804106), the Fondation Jean-Marie Lehn, the French National Research Agency (ANR LabEx “Chemistry of Complex Systems” ANR-10-IDEX-0002, and a PhD fellowship for B.L. under contract ANR-17-EURE-0016), and the Morrell Fund, Yusuf Hamied Department of Chemistry. We thank D. Lichosyt (University of Strasbourg) for preliminary studies of Ru-/Pd- dual relay using rac-btfm-garphos, and A. Bond (University of Cambridge) for X-ray crystallography.

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: C–H bond functionalisation · relay catalysis · dynamic kinetic resolution · enantioselective reactions · transition metal catalysis

- [1] a) T. L. Lohr, T. J. Marks, *Nat. Chem.* **2015**, *7*, 477; b) S. Martínez, L. Veth, B. Lainer, P. Dydio, *ACS Catal.* **2021**, *11*, 3891; c) B. Lainer, K. Das, P. Dydio, *Chem. Commun.* **2023**, *59*, 4716; d) H. Pellissier, *Adv. Synth. Catal.* **2020**, *362*, 2289; e) S. P. Sancheti, Urvashi, M. P. Shah, N. T. Patil, *ACS Catal.* **2020**, *10*, 3462; f) F. Rudroff, M. D. Mihovilovic, H. Gröger, R. Snajdrova, H. Iding, U. T. Bornscheuer, *Nat. Catal.* **2018**, *1*, 12; g) F. Romiti, J. del Pozo, P. H. S. Paioti, S. A. Gonsales, X. Li, F. W. W. Hartrampf, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 17952; h) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866; i) S. M. Inamdar, V. S. Shinde, N. T. Patil, *Org. Biomol. Chem.* **2015**, *13*, 8116; j) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211; k) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633; l) L. M. Ambrosini, T. H. Lambert, *ChemCatChem* **2010**, *2*, 1373; m) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; n) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; o) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365.
- [2] a) A. S. Goldman, A. H. Roy, Z. Huang, W. Schinski, M. Brookhart, *Science* **2006**, *312*, 257; b) M. C. Haibach, S. Kundu, M. Brookhart, A. S. Goldman, *Acc. Chem. Res.* **2012**, *45*, 947.
- [3] a) R. J. Conk, S. Hanna, J. X. Shi, J. Yang, N. R. Ciccio, L. Qi, B. J. Bloomer, S. Heuvel, T. Wills, J. Su, A. T. Bell, J. F. Hartwig, *Science* **2022**, *377*, 1561; b) N. M. Wang, G. Strong, V. DaSilva, L. Gao, R. Huacuja, I. A. Konstantinov, M. S. Rosen, A. J. Nett, S. Ewart, R. Geyer, S. L. Scott, D. Guironnet, *J. Am. Chem. Soc.* **2022**, *144*, 18526.
- [4] a) Y. Yuki, K. Takahashi, Y. Tanaka, K. Nozaki, *J. Am. Chem. Soc.* **2013**, *135*, 17393; b) Z. Jia, G. Shan, C. G. Daniliuc, A. P. Antonchick, H. Waldmann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14493; c) C. A. Denard, M. J. Bartlett, Y. Wang, L. Lu, J. F. Hartwig, H. Zhao, *ACS Catal.* **2015**, *5*, 3817; d) Z. C. Litman, Y. Wang, H. Zhao, J. F. Hartwig, *Nature* **2018**, *560*, 355.
- [5] D. Lichosyt, Y. Zhang, K. Hurej, P. Dydio, *Nat. Catal.* **2019**, *2*, 114.
- [6] W. Miao, J. Zhang, Y. Yang, W. Tang, D. Xue, J. Xiao, H. Sun, C. Wang, *Angew. Chem. Int. Ed.* **2023**, *62*, e202306015.
- [7] D. A. Culklin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234.
- [8] For the seminal report in stereoselective hydrogenation of carbonyl compounds under dynamic kinetic resolution, see: a) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *J. Am. Chem. Soc.* **1989**, *111*, 9134; for a leading review, see: b) V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528.
- [9] J.-H. Xie, Z.-T. Zhou, W.-L. Kong, Q.-L. Zhou, *J. Am. Chem. Soc.* **2007**, *129*, 1868.
- [10] X. Li, B. List, *Chem. Commun.* **2007**, 1739.
- [11] J. A. Friest, Y. Maezato, S. Broussy, P. Blum, D. B. Berkowitz, *J. Am. Chem. Soc.* **2010**, *132*, 5930.
- [12] a) B. G. Reed-Berendt, D. E. Latham, M. B. Dambatta, L. C. Morrill, *ACS Cent. Sci.* **2021**, *7*, 570; b) A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410; c) Y. Obora, *ACS Catal.* **2014**, *4*, 3972–3981.
- [13] a) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082–; b) Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou, J.-S. Yu, *ACS Catal.* **2020**, *10*, 955; c) Y. Terao, Y. Fukuoka, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2002**, *43*, 101; d) R. Martín, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7236; e) G. D. Vo, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2008**, *47*, 2127; f) J. García-Fortanet, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 8108; g) P. Nareddy, L. Mantilli, L. Guénée, C. Mazet, *Angew. Chem. Int. Ed.* **2012**, *51*, 3826; h) Z. Pan, W. Li, S. Zhu, F. Liu, H. Wu, J. Zhang, *Angew. Chem. Int. Ed.* **2021**, *60*, 18542.
- [14] a) T. W. Ng, G. Liao, K. K. Lau, H. Pan, Y. Zhao, *Angew. Chem. Int. Ed.* **2020**, *59*, 11384; b) R. Xu, K. Wang, H. Liu, W. Tang, H. Sun, D. Xue, J. Xiao, C. Wang, *Angew. Chem. Int. Ed.* **2020**, *59*, 21959.
- [15] a) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2010**, *132*, 11592; b) A. A. Friedman, J. Panteleev, J. Tsoung, V. Huynh, M. Lautens, *Angew. Chem. Int. Ed.* **2013**, *52*, 9755; c) L. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 13850; d) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712.
- [16] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621.
- [17] P. Weber, A. Biafora, A. Doppiu, H.-J. Bongard, H. Kelm, L. J. Gooßen, *Org. Process Res. Dev.* **2019**, *23*, 1462.
- [18] C. G. Wermuth, Ed., *The Practice of Medicinal Chemistry*, Academic, Amsterdam; London, **2003**.
- [19] a) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260; b) S. Guduguntla, M. Fañanás-Mastral, B. L. Feringa, *J. Org. Chem.* **2013**, *78*, 8274; c) Q. Wang, X. Liu, X. Liu, B. Li, H. Nie, S. Zhang, W. Chen, *Chem. Commun.* **2014**, *50*, 978; d) S. H. Lau, M. A. Borden, T. J. Steiman, L. S. Wang, M. Parasram, A. G. Doyle, *J. Am. Chem. Soc.* **2021**, *143*, 15873.

Manuscript received: May 3, 2024

Accepted manuscript online: May 27, 2024

Version of record online: July 10, 2024