



HAL
open science

Merging Iridium-Catalyzed Stereoselective Coupling from Alcohols with Organocatalytic Functionalization at the Aldehyde Oxidation Level

Anestis Alexandridis, Adrien Quintard

► **To cite this version:**

Anestis Alexandridis, Adrien Quintard. Merging Iridium-Catalyzed Stereoselective Coupling from Alcohols with Organocatalytic Functionalization at the Aldehyde Oxidation Level. *ACS Catalysis*, 2023, 13 (22), pp.14945-14952. 10.1021/acscatal.3c04286 . hal-04426368

HAL Id: hal-04426368

<https://hal.science/hal-04426368>

Submitted on 30 Jan 2024

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.

Merging Iridium-Catalyzed Stereoselective Coupling from Alcohols with Organocatalytic Functionalization at the Aldehyde Oxidation Level

Anestis Alexandridis,^a Adrien Quintard^{a*}

^aUniv. Grenoble Alpes, CNRS, DCM, 38000 Grenoble, France

ABSTRACT: We report the selective merging between a Krische-type iridium-catalyzed C–C coupling and an organocatalyzed oxa-Michael addition. Such a general strategy triggers the direct double functionalization of alcohols through a complex multicatalytic pathway merging the two catalytic cycles in one. The iridium catalyst dehydrogenates the alcohol to an aldehyde which is intercepted in an organocatalyzed functionalization. Meanwhile, the generated iridium hydride activates a pro-nucleophile to subsequently create the final chiral alcohol through a stereoselective C–C coupling on the functionalized aldehyde. The disclosed multicatalytic reaction, fulfilling all the principles of redox economy, enables the stereoselective preparation of complex tetrahydropyrans, scaffolds present in numerous natural products and featuring up to three controlled stereogenic centers.

KEYWORDS: Iridium catalysis, organocatalysis, multicatalysis, hydrogen transfer, redox economies.

INTRODUCTION

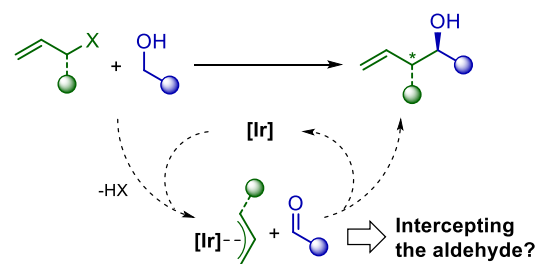
Chiral alcohols are ubiquitous in natural products and drugs, and developing efficient methods for their eco-compatible synthesis represents an ongoing challenge. Due to the inherent lack of electrophilicity of the alcohol-bearing carbon, their construction often relies on chemical modification at the carbonyl oxidation level (e.g. aldehyde). This requires additional and undesirable waste-generating redox steps to adjust the carbon chain oxidation level.¹

Catalytic dehydrogenation of alcohols is an excellent tool to generate in a waste-free manner reactive carbonyl compounds for their in-situ derivatization.² Taking advantage of this reactivity, a broad array of transformations directly modifying alcohols through activation by dehydrogenation and subsequent functionalization at the carbonyl oxidation level have been developed. In this context, the group of Krische discovered a wide variety of useful C–C coupling reactions enabling the transformation of primary alcohols into enantioenriched secondary alcohols (Figure 1a).^{3,4} These transformations, catalyzed by chiral iridium or ruthenium complexes, are based on mechanisms involving the formation and functionalization of transient aldehydes. Initial dehydrogenation by the metal complex generates the reactive carbonyl compound, while the metal-hydride inserts in the carbon pro-nucleophile, thus generating the nucleophilic organometallic reagent. Stereoselective addition on the aldehyde generates the desired secondary alcohols. Among the numerous advantages of the above-mentioned methods, primary alcohols are directly transformed into enantioenriched secondary alcohols without requiring any stoichiometric redox reagents; the C–C couplings avoid the use of air-, moisture-sensitive and potentially pyrophoric organometallic reagents (Grignard and organolithium reagents, among others); the stereoselectivity of the reactions is usually excellent.

Given the formation of intermediate aldehydes in Krische-type catalytic cycles, it would be of great interest to intercept these transient reactive species in an additional functionalization

process. Through strategically merging two catalytic cycles, such a strategy would directly construct chiral secondary alcohols of additional complexity through two distinct – yet interwoven – functionalization events, starting from simple primary alcohols.

a) Krische C-C couplings from alcohols using allyl donors:



b) Proposed multicatalytic functionalization:

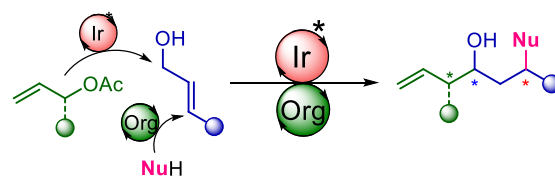


Figure 1. Using alcohols for reductive couplings (a) and proposed multicatalytic functionalization (b).

It is well known that secondary amines are excellent for the selective functionalization of aldehydes through enamine or iminium type catalysis.⁵ Therefore we hypothesized that a multicatalytic strategy,^{6,7} combining the iridium-catalyzed stereoselective C–C coupling from alcohols with the organocatalyzed interception of the aldehyde intermediate, could trigger the desired alcohol multiple functionalization (Figure 1b). Aside from the potential catalysts and reaction partners compatibilities, an additional, considerable challenge – in this type of merged catalytic cycle mechanisms – lies in the presence of only a small amount of carbonyl intermediate, corresponding at most to the amount of iridium catalyst. This can potentially strongly impact the kinetics of the desired in-situ aldehyde

functionalization,⁸ which should be faster than the direct trapping by the organometallic nucleophile. Moreover, the generated iridium π -allyls are renowned for their electrophilicity towards the addition of various nucleophilic amines; an additional challenge which could rapidly inhibit the organocatalytic activity.⁹

In order to develop the hypothesized reactivity, we decided to focus on an intramolecular approach with functionalization via an oxa-Michael addition, commonly catalyzed by various secondary amine organocatalysts (Figure 2).¹⁰ Developing such a transformation would require to accommodate the presence of an existing chiral secondary alcohol on the starting material.¹¹ If successful, it would provide a direct access to scaffolds containing both the chiral secondary alcohol and a tetrahydropyran (THP) core (Figure 2). A reaction of this kind would be of great synthetic interest given the prevalence of this pattern, frequently encountered in bioactive natural products such as Enigmazole A, Phorboxazole A, Spirastrellolide A, or Exiguolide among others.¹² Herein, we report our success at developing this envisioned transformation, which should pave the way for the invention of other related reactions.

Multicatalytic Iridium C-C Coupling / Organocatalytic oxa-Michael Addition

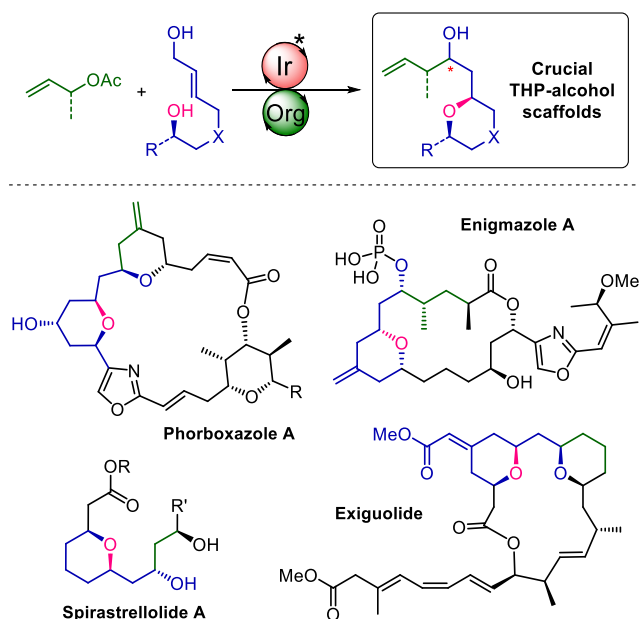


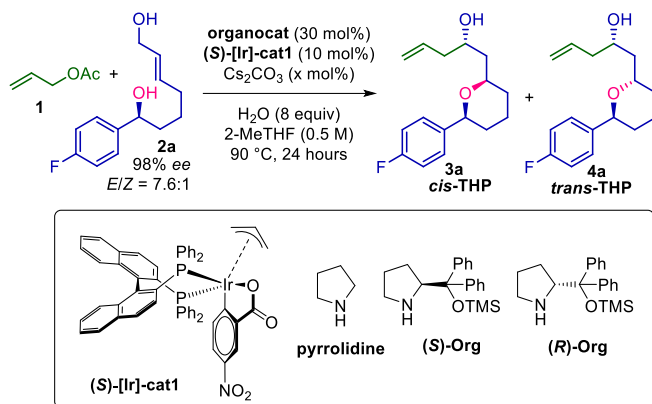
Figure 2. Developed transformation and importance of the obtained scaffolds.

RESULTS AND DISCUSSION

Optimization of the transformation was performed on the allylation of model enantioenriched (98% *ee*) diol **2a** (Table 1, see supporting information for additional optimization experiments). Among the important parameters, we found that the structure of the chiral iridium complex was crucial for optimal results. While literature reports used iridacycles featuring several electron-withdrawing substituents for optimal allylation kinetics,^{3,4} in the present transformation, these catalysts favored a too rapid C–C bond formation, preventing the oxa-Michael addition from taking place (cf. Table S1). Therefore, a single NO₂ group on the benzoate ligand was sufficient to induce the reaction with appropriate

kinetics for both alcohol dehydrogenation and the resulting aldehyde allylation upon oxa-Michael cyclization. Similarly, the use of BINAP instead of other ligands (such as SEGPHOS) also provided better reactivity, and **(S)-[Ir]-cat1** was found to be optimal towards the formation of the expected functionalized *cis*-THP.

Table 1. Selected optimization experiments.



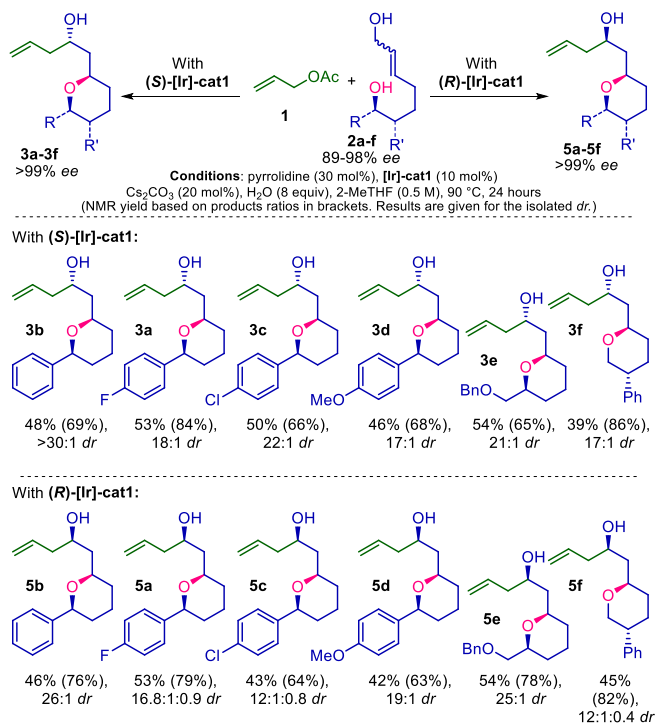
Entry	Organocat.	Cs ₂ CO ₃ (x mol%)	<i>cis</i> -THP (<i>dr</i>) ^[a]	<i>trans</i> -THP (<i>dr</i>) ^[a]	NMR Yield _J ^[b]
1	None	20	3.5 (5.8 : 1)	1.0 (7.5 : 1)	51%
2	(S)-Org	20	22.3 (4.3 : 1)	1.0 (3 : 1)	76%
3	(R)-Org	20	21.8 (5.4 : 1)	1.0 (5.8 : 1)	58%
4	pyrrolidine	20	24.8 (12.3 : 1)	1.0 (4.9 : 1)	84% (53%^[c])
5	pyrrolidine	80	6.6 (10.3 : 1)	1.0 (8.9 : 1)	48%
6 ^[d]	pyrrolidine	20	20.7 (12.3 : 1)	1.0 (4.6 : 1)	80%

^[a] *dr* for the relative configuration at the alcohol stereocenter with respect to the given THP. ^[b] NMR yield for *cis*-THP estimated from the ¹⁹F NMR ratio of products. ^[c] Isolated yield. Isolated *dr* = 18 : 1. Product isolated in >99% *ee*. ^[d] Starting from a 2.6:1 E/Z ratio of starting material (2 equivalents of water).

In the absence of any secondary amine organocatalyst, the *cis*-THP was observed in only 51% NMR yield and with a moderate 3.5:1 ratio with the *trans*-THP (Table 1, entry 1). In the presence of chiral **(S)-Org**, the process was considerably improved, providing the selective formation of the *cis*-THP over the *trans*-one in 76% NMR yield. Interestingly, despite its inherent nucleophilicity, the secondary amine organocatalyst is compatible with the reaction conditions, and most importantly, the diastereocontrol towards the formation of the *cis*-THP was considerably improved to a 22.3:1 ratio (entry 2). A clear mismatch effect was observed with **(R)-Org**, leading to a lower 58% NMR yield (entry 3), despite the lower reactivity, the formation of the *cis*-THP was still favored in a 21.8:1 ratio. This result indicates the stereocontrol mode of action by the organocatalyst. Through the formation of the iminium ion, the organocatalyst does not control the enantiofacial discrimination during the cyclization, but favors the equilibrium towards the more stable *cis*-THP through accelerated reversible oxa-

Michael cyclization.¹⁰ This was confirmed when pyrrolidine was used as organocatalyst (entry 4). Use of this achiral catalyst provided an optimal 84% NMR yield (53% isolated) and excellent 24.8:1 *cis*-THP / *trans*-THP ratio. Through all this study, the difference between NMR and isolated yields is due to partial products loss during the silica gel chromatographic separation with the minor impurities. Importantly, the product was isolated in 99% *ee*, confirming the absence of racemization of the chiral benzylic alcohol by the iridium complex. The effect of pyrrolidine was further confirmed when increasing the amount of base to 80 mol% (entry 5) which provided a lower 6.6:1 *cis*-THP / *trans*-THP ratio, possibly through a rapid and irreversible, base-induced oxa-Michael cyclization. In agreement with the described catalyst effects, modifying the (*S*)-[Ir]-cat1 / pyrrolidine ratio (see Table S6), also strongly impacted the diastereocontrol. Finally, starting from a diol substrate with 2.6:1 *E/Z* ratio, provided with equal efficiency the same *cis*-THP as starting from a diol substrate with 7.6:1 *E/Z* ratio (entries 4 and 6). This confirms a mechanism involving the formation of the intermediate α,β -unsaturated aldehyde, rapidly equilibrating through the action of pyrrolidine to the *cis*-THP prior to the C–C bond formation.¹³

With the optimal conditions using allyl acetate in hand, the scope of the transformation was studied using various diol substrates and carbon pro-nucleophiles. The multicatalytic conditions triggered the efficient formation of a wide variety of THP scaffolds.



Scheme 1. Alkylation scope of the multicatalyzed process.

Using allyl acetate **1** as pro-nucleophile and (*S*)-[Ir]-cat1 (Scheme 1), *cis*-THP **3a-d** were generated with equal efficiency from various benzylic alcohols. An aliphatic secondary alcohol was also well tolerated, constructing **3e** possessing an additional ether functional group. Finally, the multicatalytic reaction was tested on a challenging substrate possessing two primary alcohols, one aliphatic and one allylic. Gratifyingly, the expected cyclization /allylation

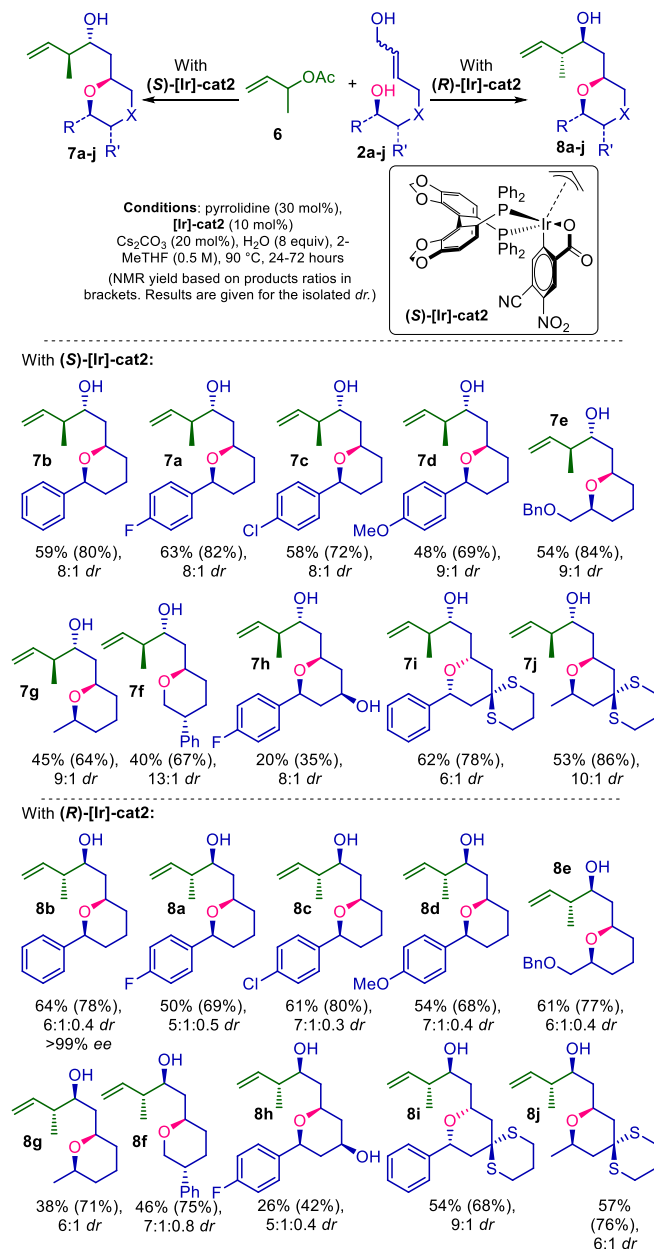
product **3f** was generated selectively, indicating a strong preference for the dehydrogenation of the allylic alcohol over the aliphatic one. In addition, the configuration at the phenyl-bearing carbon induced a selective ring closure, favoring the formation of the THP with all substituents in equatorial positions.

Inverting the configuration of the iridium complex, the diastereodivergence of the transformation was confirmed, leading to the opposite configuration at the alcohol stereocenter. Using (*R*)-[Ir]-cat1, all corresponding products **5a-f** were obtained with similar efficiency, indicating a perfect catalyst control during the C–C bond-forming step. These multi-functionalized products were obtained in more than 99% *ee*, confirming that the stereochemical integrity of the secondary alcohols is preserved during the transformation. In addition, since the starting diols were not enantiopure (89-98% *ee*), this perfect enantioselectivity is indicative of an amplification of chirality during the chiral iridium catalyzed C–C bond forming event.

The crotylation of alcohols was then performed employing racemic 1-methylallyl acetate **6** as crotyl donor (Scheme 2). It was found that the use of (*S*)-[Ir]-cat2 was mandatory to observe the formation of the expected multiple functionalization product, indicative of a slower C–C bond formation with this more hindered pro-nucleophile. Through the multicatalytic pathway, a great variety of valuable chiral tetrahydropyrans was generated through the control of three new stereogenic centers. Most importantly, the stereoselectivity of the crotylation was once again controlled in a diastereodivergent manner using either (*S*)- or (*R*)-[Ir]-cat2. The reaction scope included tetrahydropyrans **7a-e,g** and **8a-e,g** prepared from benzylic or aliphatic alcohols. As was the case for the allylation/cyclization, engaging a substrate containing two primary alcohols proved to be selective for the formation of tetrahydropyrans **7f** and **8f**. 4-substitution of the tetrahydropyran's core, which could provide scaffolds of different natural products such as Phorboxazole A, Exiguolide or Enigmazole A was then studied. Preparation of the challenging 4-substituted tetrahydropyrans **7h** and **8h** featuring an additional unprotected chiral secondary alcohol proved more difficult and provided lower conversion even though the expected product was isolated with good stereocontrol. Substituting the 4-position with a dithiane, gave rise to complex spiro-tetrahydropyrans **7i-j** and **8i-j**, despite the presence of the thioethers, renowned for potentially interfering with transition metal-catalyzed processes.

Reverse prenylation using 1,1-dimethylallene,¹⁴ constructed the *cis*-THPs **10b-11b** possessing a new quaternary center (Scheme 3). This reaction occurs under mild conditions and – unlike the transformations described previously – does not require an exogenous base. Controlled by the organocatalyst, the *cis*-THP is selectively generated with perfect diastereocontrol while the iridium complex controls the stereochemistry on the newly formed alcohol albeit with lower efficiency (3:1 *dr*). Most importantly, a control experiment in the absence of pyrrolidine once again confirmed the crucial role of the organocatalyst for the rapid oxa-Michael addition. Indeed, excluding this catalyst only provided the product of direct C–C bond formation **12**.

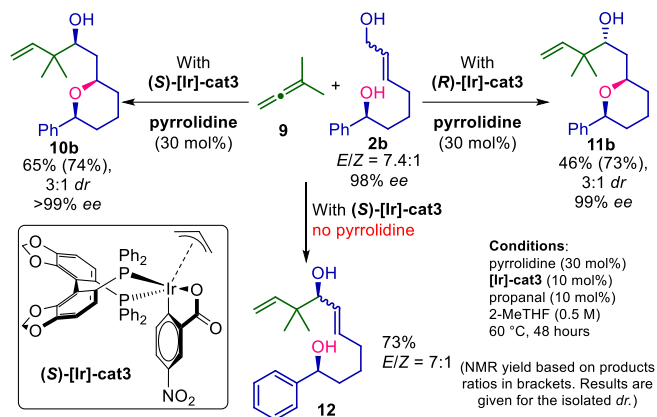
Moreover, the *E/Z* ratio of the alkene was kept unchanged confirming the role of the organocatalyst over the alkene isomerization. Finally, first attempt at using an achiral alcohol with this system did not provide any enantiocontrol by a chiral organocatalyst (See Supporting Information).



Scheme 2. Crotylation scope of the multicatalyzed process.

Altogether, these experiments confirm the general mechanism shown in Scheme 4, describing the allylation reaction, based on the well-studied iridium catalyzed C-C coupling.⁴ From the iridium precatalyst [Ir]-Cat, coordination of the alcohol and release of propene provides the alkoxide complex. Dehydrogenation forms the iridium hydride in equilibrium with the anionic iridium complex. Accumulation of acetic acid is not detrimental to the favored formation of this specie, subsequently generating the required nucleophilic π -allyl upon insertion on allyl acetate. On the other side, the secondary amine reacts with the liberated aldehyde. This generates the electrophilic iminium ion prone to

the oxa-Michael addition, affording after organocatalyst liberation, the aldehyde featuring the *cis*-THP ring. This aldehyde then reacts with the iridium π -allyl to generate in a diastereoselective manner the desired secondary alcohol upon ligand exchange with a new molecule of starting alcohol. As a result, in this mechanism clearly distinct from a sequential multicatalytic cycle, the two catalytic cycles are merged in one, to provide through the different catalytic intermediates, complex alcohols by a double functionalization of allylic alcohols.

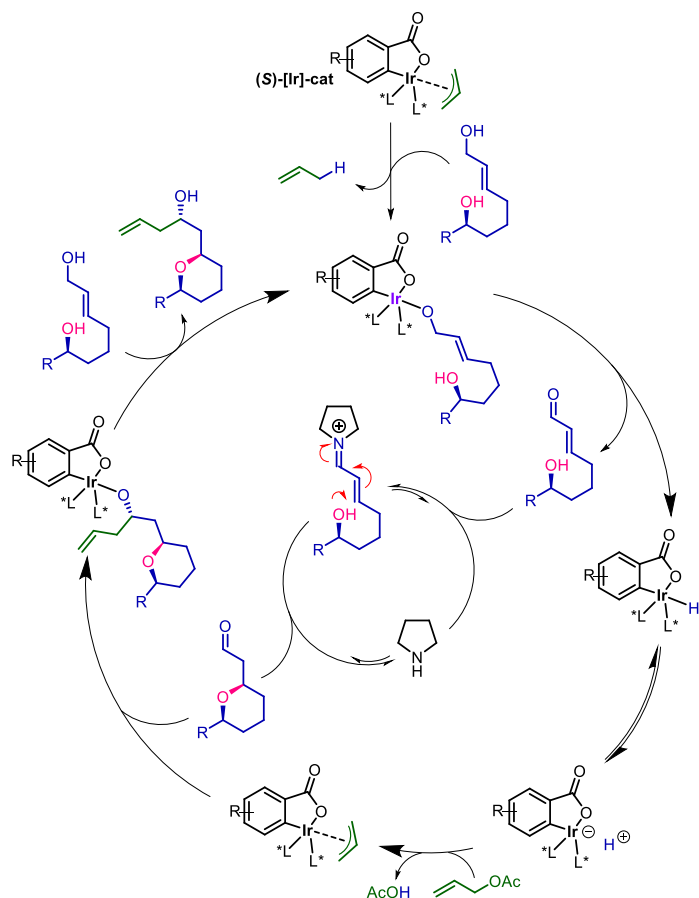


Scheme 3. Reverse prenylation multicatalyzed process. 3:1 *dr* arising from the lower stereocontrol during the iridium catalyzed C-C bond formation. Reaction leading to **10b** performed on a 1 mmol scale.

CONCLUSION

To conclude, by appropriately merging two compatible catalytic cycles, alcohols have been functionalized twice to construct directly complex adducts featuring up to three stereogenic centers controlled in a diastereodivergent manner. This multicatalytic strategy is possible by interlocking an iridium-catalyzed C-C coupling starting from an alcohol, forming a small amount of aldehyde with an iminium type organocatalytic cycle intercepting the aldehyde and increasing its complexity.

The demonstration of such a principle in an intramolecular oxa-Michael addition enables the generation of functionalized tetrahydropyrans, scaffolds of interest present in numerous bioactive natural products. The reaction was found to be general and selectively functionalizing the allylic alcohols. The discovery of such multicatalytic combinations should rapidly find implications in the exploration of other couplings, in natural product synthesis, but should also inspire chemists to investigate new synthetic strategies merging several catalytic cycles.



Scheme 4. Proposed general mechanism of the multicatalytic reaction.

AUTHOR INFORMATION

Corresponding Author

Adrien Quintard

Univ. Grenoble Alpes, CNRS, DCM, 38000 Grenoble, France
 orcid.org/0000-0003-0193-6524

Email : adrien.quintard@univ-grenoble-alpes.fr

Author

Anestis Alexandridis

Univ. Grenoble Alpes, CNRS, DCM, 38000 Grenoble, France

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

The Agence Nationale de la Recherche (ANR-19-CE07-0033), the Centre National de la Recherche Scientifique (CNRS), Université Grenoble-Alpes, are warmly acknowledged for financial support.

ASSOCIATED CONTENT

Experimental protocols, detailed analysis, additional optimization experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

ACKNOWLEDGMENT

We would like to thank Elie Vincent and Martin Fayolle for their help in the synthesis of two starting diols.

REFERENCES

- (1) For the concept of redox economy in synthesis, see: a) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. Redox economy in organic synthesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854-2867; b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3010-3021.
- (2) For selected general reviews on reactions initiated by alcohols dehydrogenation, see: a) Gunanathan, C.; Milstein, D. Applications of acceptorless dehydrogenation and related transformations in chemical synthesis. *Science*, **2013**, *341*, 1229712-1229721; b) Yang, Q.; Wang, Q. Yu, Z. Substitution of alcohols by N-nucleophiles via transition metal-catalyzed dehydrogenation. *Chem. Soc. Rev.* **2015**, *44*, 2305-2329; c) Quintard, A.; Rodriguez, J. Catalytic enantioselective OFF \leftrightarrow ON activation processes initiated by hydrogen transfer: concepts and challenges. *Chem. Commun.* **2016**, *52*, 10456-10473; d) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410-1459; e) Reed-Berendt, B. G.; Latham, D. E.; Dambatta, M. B.; Morrill, L. C. Borrowing Hydrogen for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7*, 570-585.
- (3) For recent reviews, see: a) Feng, J.; Kasun, Z. A.; Krische, M. J. Enantioselective Alcohol C-H Functionalization for Polyketide Construction: Unlocking Redox-Economy and Site-Selectivity for Ideal Chemical Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 5467-5478; b) Kim, S. W.; Zhang, W.; Krische, M. J. Catalytic Enantioselective Carbonyl Allylation and Propargylation via Alcohol-Mediated Hydrogen Transfer: Merging the Chemistry of Grignard and Sabatier. *Acc. Chem. Res.* **2017**, *50*, 2371-2380; c) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-catalyzed reductive coupling of olefin-derived nucleophiles: Reinventing carbonyl addition. *Science* **2016**, *354*, 300-308; d) Gazolla Santana, C.; Krische, M. J. From Hydrogenation to Transfer Hydrogenation to Hydrogen Auto-Transfer in Enantioselective Metal-Catalyzed Carbonyl Reductive Coupling: Past, Present, and Future. *ACS Catal.* **2021**, *11*, 5572-5585.
- (4) For selected examples, see: a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate. *J. Am. Chem. Soc.* **2008**, *130*, 6340-6341; b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Allyl Acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition. *J. Am. Chem. Soc.* **2008**, *130*, 14891-14899; c) Kim, I. S.; Han, S. B.; Krische, M. J. *anti*-Diastereo- and Enantioselective Carbonyl Crotylation from the Alcohol or Aldehyde Oxidation Level Employing a Cyclometallated Iridium Catalyst: α -Methyl Allyl Acetate as a Surrogate to Preformed Crotylmetal Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 2514-2520; d) Gao, X.; Townsend, I. A.; Krische, M. J. Enhanced *anti*-Diastereo- and Enantioselectivity in Alcohol-Mediated Carbonyl Crotylation Using an Isolable Single Component Iridium Catalyst. *J. Org. Chem.* **2011**, *76*, 2350-2354; e) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. Protecting-Group-Free Diastereoselective C-C Coupling of 1,3-Glycols and Allyl Acetate through Site-Selective Primary Alcohol Dehydrogenation. *Angew. Chem., Int. Ed.* **2013**, *52*, 3195-3198; f) Feng, J.; Garza, V. J.; Krische, M. J. Redox-Triggered C-C Coupling of Alcohols and Vinyl Epoxides: Diastereo- and Enantioselective Formation of All-Carbon Quaternary Centers via *tert*-(Hydroxy)-Prenylation. *J. Am. Chem. Soc.* **2014**, *136*, 8911-8914.

- (5) For a selected review, see: Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171.
- (6) For reviews on multicatalysis, see: a) Inamdar, S. M.; Shinde, V. S.; Patil, N. T. Enantioselective cooperative catalysis. *Org. Biomol. Chem.* **2015**, *13*, 8116–8162; b) Afewerki, S.; Córdova, A. Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chem. Rev.* **2016**, *116*, 13512–13570; c) Krautwald, S.; Carreira, E. M. Stereodivergence in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5627–5639. d) Quintard, A. Iron-Based Multi-Catalysis: Eco-Compatible Alternative for Complex Molecules Synthesis. *Chem. Eur. J.* **2021**, *27*, 89–105; e) Martínez, S.; Veth, L.; Lainer, B.; Dydio, P. Challenges and Opportunities in Multicatalysis. *ACS Catal.* **2021**, *11*, 3891–3915; f) Chen, D.-F.; Gong, L.-Z. Organo/Transition-Metal Combined Catalysis Rejuvenates Both in Asymmetric Synthesis. *J. Am. Chem. Soc.* **2022**, *144*, 2415–2437; g) Lainer, B.; Das, K.; Dydio, P. Variable structure diversification by multicatalysis: the case of alcohols. *Chem. Commun.* **2023**, *59*, 4716–4725.
- (7) For literature examples on the combination between reversible catalytic alcohol dehydrogenation such as borrowing hydrogen and catalytic carbonyl compound functionalization, see: a) Quintard, A.; Constantieux, T.; Rodriguez, J. An Iron/Amine-Catalyzed Cascade Process for the Enantioselective Functionalization of Allylic Alcohols. *Angew. Chem. Int. Ed.* **2013**, *52*, 12883–12887; b) Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. Enantioselective Cascade Formal Reductive Insertion of Allylic Alcohols into the C(O)–C Bond of 1,3-Diketones: Ready Access to Synthetically Valuable 3-Alkylpentanol Units. *Org. Lett.* **2014**, *16*, 2802–2805; c) Quintard, A.; Roudier, M.; Rodriguez, J. Multicatalytic Enantioselective Borrowing Hydrogen δ -Lactonization Strategy from β -Keto Esters and Allylic Alcohols. *Synthesis*. **2018**, *50*, 785–792; d) Lichosyt, D.; Zhang, Y.; Hurej, K.; Dydio, P. Dual-catalytic transition metal systems for functionalization of unreactive sites of molecules. *Nature Catalysis* **2019**, *2*, 114–122; e) Xu, R.; Wang, K.; Liu, H.; Tang, W.; Sun, H.; Xue, D.; Xiao, J.; Wang, C. Anti-Markovnikov Hydroamination of Racemic Allylic Alcohols to Access Chiral γ -Amino Alcohols. *Angew. Chem. Int. Ed.* **2020**, *59*, 21959–21964; c) Pan, Y.; You, Y.; He, D.; Chen, F.; Chang, X.; Jin, M. Y.; Xing, X. Asymmetric Synthesis of γ -Secondary Amino Alcohols via a Borrowing-Hydrogen Cascade. *Org. Lett.* **2020**, *22*, 7278–7283; d) Li, F.; Long, L.; He, Y.-M.; Li, Z.; Chen, H.; Fan, Q.-H. Manganese-Catalyzed Asymmetric Formal Hydroamination of Allylic Alcohols: A Remarkable Macrocyclic Ligand Effect. *Angew. Chem. Int. Ed.* **2022**, *61*, e202202972; e) Zhang, X.; Ma, W.; Zhang, J.; Tang, W.; Xue, D.; Xiao, J.; Sun, H.; Wang, C. Asymmetric Ruthenium-Catalyzed Hydroalkylation of Racemic Allylic Alcohols for the Synthesis of Chiral Amino Acid Derivatives. *Angew. Chem. Int. Ed.* **2022**, *61*, e202203244; f) Chang, X.; Cheng, X.; Liu, X. T.; Fu, C.; Wang, W.-Y.; Wang, C.-J. Stereodivergent Construction of 1,4-Nonadjacent Stereocenters via Hydroalkylation of Racemic Allylic Alcohols Enabled by Copper/Ruthenium Relay Catalysis. *Angew. Chem. Int. Ed.* **2022**, *61*, e202206517; g) Jin, M. Y.; Zhou, Y.; Xiao, D.; You, Y.; Zhen, Q.; Tao, G.; Yu, P.; Xing, X. Simultaneous Kinetic Resolution and Asymmetric Induction within a Borrowing Hydrogen Cascade Mediated by a Single Catalyst. *Angew. Chem. Int. Ed.* **2022**, *61*, e202112993. For selected examples combining aminocatalysis and electrophilic iridium π -allyl: h) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio- and Diastereodivergent Dual Catalysis: α -Allylation of Branched Aldehydes. *Science*, **2013**, *340*, 1065–1068; i) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. Stereodivergent α -Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 3020–3023.
- (8) Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. Triple Iron/Copper/Iminium Activation for the Efficient Redox Neutral Catalytic Enantioselective Functionalization of Allylic Alcohols. *ACS Catal.* **2016**, *6*, 5236–5244.
- (9) For the reactivity of such iridium π -allyl towards nucleophilic addition: a) Meza, T.; Wurm, T.; Smith, L.; Kim, S. W.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Amphiphilic π -Allyliridium C,O-Benzoates Enable Regio- and Enantioselective Amination of Branched Allylic Acetates Bearing Linear Alkyl Groups. *J. Am. Chem. Soc.* **2018**, *140*, 1275–1279; b) Kim, S. W.; Wurm, T.; Brito, G. A.; Jung, W.-O.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Hydroamination versus Allylic Amination in Iridium-Catalyzed Reactions of Allylic Acetates with Amines: 1,3-Aminoalcohols via Ester-Directed Regioselectivity. *J. Am. Chem. Soc.* **2018**, *140*, 9087–9090; c) Kim, S. W.; Schwartz, L. A.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Regio- and Enantioselective Iridium-Catalyzed Amination of Racemic Branched Alkyl-Substituted Allylic Acetates with Primary and Secondary Aromatic and Heteroaromatic Amines. *J. Am. Chem. Soc.* **2019**, *141*, 671–676; d) Kim, S. W.; Schempp, T. T.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Regio- and Enantioselective Iridium-Catalyzed N-Allylation of Indoles and Related Azoles with Racemic Branched Alkyl-Substituted Allylic Acetates. *Angew. Chem. Int. Ed.* **2019**, *58*, 7762–7766.
- (10) a) Díez, D.; Núñez, M. G.; Benítez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. Organocatalytic Synthesis of an Alkyltetrahydropyran. *Synlett*, **2009**, *3*, 390–394; b) McGarraugh, P. G.; Brenner-Moyer, S. E. An Organocascade Kinetic Resolution. *Org. Lett.* **2011**, *13*, 6460–6463; c) McGarraugh, P. G.; Johnston, R. C.; Martinez-Munoz, A.; Cheong, P. H.-Y.; Brenner-Moyer, S. E. Organocatalytic Kinetic Resolution Cascade Reactions: New Mechanistic and Stereochemical Manifold in Diphenyl Prolinol Silyl Ether Catalysis. *Chem. Eur. J.* **2012**, *18*, 10742–10752; d) Lee, K.; Kim, H.; Hong, J. Stereoselective Synthesis of Tetrahydropyrans through Tandem and Organocatalytic Oxa-Michael Reactions: Synthesis of the Tetrahydropyran Cores of ent-(+)-Sorangicin A. *Eur. J. Org. Chem.* **2012**, 1025–1032; e) Lanier, M. L.; Kasper, A. C.; Kim, H.; Hong, J. Synthesis of α,α' -trans-Oxepanes through an Organocatalytic Oxa-conjugate Addition Reaction. *Org. Lett.* **2014**, *16*, 2406–2409; f) Nicolaou, K. C.; Rhoades, D.; Kumar, S. M. Total Syntheses of Thailanstatins A–C, Spliceostatin D, and Analogues Thereof. Stereodivergent Synthesis of Tetrasubstituted Dihydro- and Tetrahydropyrans and Design, Synthesis, Biological Evaluation, and Discovery of Potent Antitumor Agents. *J. Am. Chem. Soc.* **2018**, *140*, 8303–8320.
- (11) For reductive couplings involving non-protected alcohols, see: a) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. 1,*n*-Glycols as Dialdehyde Equivalents in Iridium-Catalyzed Enantioselective Carbonyl Allylation and Iterative Two-Directional Assembly of 1,3-Polyols. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018–5021; b) Hassan, A.; Lu, Y.; Krische, M. J. Elongation of 1,3-Polyols via Iterative Catalyst-Directed Carbonyl Allylation from the Alcohol Oxidation Level. *Org. Lett.* **2009**, *11*, 3112; c) Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. Total Synthesis of (+)-Roxatitin via C–C Bond Forming Transfer Hydrogenation: A Departure from Stoichiometric Chiral Reagents, Auxiliaries, and Premetalated Nucleophiles in Polyketide Construction. *J. Am. Chem. Soc.* **2010**, *132*, 15559–15561; d) Gao, X.; Han, H.; Krische, M. J. Direct Generation of Acyclic Polypropionate Stereopolyads via Double Diastereo- and Enantioselective Iridium-Catalyzed Crotylation of 1,3-Diols: Beyond Stepwise Carbonyl Addition in Polyketide Construction. *J. Am. Chem. Soc.* **2011**, *133*, 12795–12800; e) Shin, I.; Wang, G.; Krische, M. J. Catalyst-Directed Diastereo- and Site-Selectivity in Successive Nucleophilic and Electrophilic Allylations of Chiral 1,3-Diols: Protecting-Group-Free Synthesis of Substituted Pyrans. *Chem. Eur. J.* **2014**, *20*, 13382–13389; f) Quintard, A.; Rodriguez, J. Enantioselective Ir-Catalyzed Bidirectional Reductive Coupling. *Org. Lett.* **2019**, *21*, 453–456; g) Saldares, C.; Ortiz, E.; Santana, C. G.; Spinello, B. J.; Krische, M. J. Asymmetric Ruthenium-Catalyzed Carbonyl Allylations by Gaseous Allene via Hydrogen Auto-Transfer: 1° versus 2° Alcohol Dehydrogenation for Streamlined Polyketide Construction. *ACS Catal.* **2023**, *13*, 1662–1668.
- (12) Mandelalide B: a) Sikorska, J.; Hau, A. M.; Anklin, C.; Parker-Nance, S.; Davies-Coleman, M. T.; Ishmael, J. E.; McPhail, K. L. Mandelalides A–D, Cytotoxic Macrolides from a New Lissoclinum Species of South African Tunicate. *J. Org. Chem.* **2012**, *77*, 6066–6075. Phorbaxazole: b) Searle, P. A.; Molinski, T. F. Phorbaxazoles A and

B: potent cytostatic macrolides from marine sponge Phorbas species. *J. Am. Chem. Soc.* **1995**, *117*, 8126-8131. Leucascandrolide A:
c) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. Leucascandrolide A, a New Type of Macrolide: The first powerfully bioactive metabolite of calcareous sponges (Leucascandra caveolata, a new genus from the coral sea). *Helv. Chim. Acta* **1996**, *79*, 51-60.
D) Exiguolide: Ohta, S.; Uy, M. M.; Yanai, M.; Ohta, E.; Hirata, T.; Ikegami, S. Exiguolide, a new macrolide from the marine sponge *Geodia exigua*. *Tetrahedron Lett.* **2006**, *47*, 1957-1960. Spirastrellolide:
e) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. Spirastrellolide A, An Antimitotic Macrolide Isolated from the Caribbean Marine Sponge *Spirastrella coccinea*. *J. Am. Chem. Soc.* **2003**, *125*, 5296-5297.

(13) The rapid isomerization can occur through **trans-THP/cis-THP** equilibration by retro-oxa-Michael addition or directly at the α,β -unsaturated aldehyde level through *E/Z* isomerization. See for example: Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. Enantioselective Organocatalytic Hydride Reduction. *J. Am. Chem. Soc.* **2005**, *127*, 32-33.

(14) Han, S. B.; Kim, I-S.; Han, H.; Krische, M. J. Enantioselective Carbonyl Reverse Prenylation from the Alcohol or Aldehyde Oxidation Level Employing 1,1-Dimethylallene as the Prenyl Donor. *J. Am. Chem. Soc.* **2009**, *131*, 6916-6917. It is described that the reverse prenylation provides opposite facial selectivity during the C-C bond formation, as compared to allylation and crotylation.

