Multicatalytic Approach to One-Pot Stereoselective Synthesis of Secondary Benzylic Alcohols
Alessandra Casnati, Dawid Lichosyt, Bruno Lainer, Lukas Rainer Veth, Pawel Dydio

To cite this version:
Alessandra Casnati, Dawid Lichosyt, Bruno Lainer, Lukas Rainer Veth, Pawel Dydio. Multicatalytic Approach to One-Pot Stereoselective Synthesis of Secondary Benzylic Alcohols. Organic Letters, 2021, 23 (9), pp.3502-3506. 10.1021/acs.orglett.1c00939 . hal-03282249

HAL Id: hal-03282249
https://hal.science/hal-03282249
Submitted on 8 Jul 2021

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.
Multicatalytic Approach to One-Pot Stereoselective Synthesis of Secondary Benzylic Alcohols

Alessandra Casnati,‡ Dawid Lichosyt,‡ Bruno Lainer, Lukas Veth, and Paweł Dydio*

University of Strasbourg, CNRS, ISIS UMR 7006, 8 allée Gaspard Monge, 67000 Strasbourg, France

Keywords: multicatalysis, sequential catalysis, stereoselective synthesis, transition metal-catalysis, one-pot economy.

ABSTRACT: One-pot procedures bear the potential to rapidly build up molecular complexity without isolations and purifications of consecutive intermediates. Here we report multicatalytic protocols that convert alkenes, unsaturated aliphatic alcohols, and aryl boronic acids into secondary benzylic alcohols with high stereoselectivities (typically >95:5 er) under sequential catalysis that integrates alkene cross-metathesis, isomerization, and nucleophilic addition. Prochiral allylic alcohols can be converted to any stereoisomer of the product with high stereoselectivity (>98:2 er, >20:1 dr).

Secondary benzylic alcohols (SBAs) represent prevalent motifs of biologically active molecules and chiral building blocks for fine-chemical synthesis. Therefore, methods of their stereoselective synthesis from available starting materials are important. Asymmetric (transfer) hydrogenation proved highly effective when aryl ketones are available (Fig. 1a). In turn, enantioselective addition of an aryl nucleophile to a carbonyl bond is practical for aliphatic aldehydes as starting materials (Fig. 1b). Given the abundance of alcohols, functionalization of their C–H bonds is attractive. In that regard, Krische reported elegant enantio- and diastereoselective α-alkylation of alcohols with unsaturated hydrocarbons (e.g., dienes, enynes; Fig. 1c). Methods for α-arylation of aliphatic alcohols were recently reported by MacMillan, Lei, and Shirakaw (Fig. 1d), albeit the enantioselective variants remain yet to be developed. Besides, the stereoretentive cross-couplings to form SBAs were reported by Falck and Molander (Fig. 1e).

We envisioned that one-pot sequential catalyses could enrich the access to SBAs from other classes of readily available starting materials (Fig. 1f-h). First, we conceived the enantioselective isomerization-addition sequence for aliphatic alcohols bearing an unsaturated bond (Fig. 1f), which are common motifs in bio-derived materials (e.g., terpenols). The strategy could be further extended to abundant alkenes (Fig. 1g), given the alkene cross-metathesis, double bond isomerization, and the enantioselective addition reactions were compatible in a one-pot fashion. Also, diastereoselective synthesis of SBAs bearing two stereocenters with a 1,3-relationship could be envisioned (Fig. 1h), provided the compatibility of both chiral catalysts was ensured. Noteworthy, the execution of multicatalytic multi-step synthesis in a one-pot fashion, without or with limited intermediary work-up, proved enabling and highly advantageous from the efficiency standpoint. However, the development of such protocols with multiple transition-metal catalyzed reactions operating in one vessel remains challenging. The prospective cross-reactivity is likely to hinder the required activity. In asymmetric reactions, any exchange of ligands is likely to deteriorate the stereoselectivity. Therefore, careful selection of catalysts and conditions is critical.

Here we report sequential multi-step protocols with up to 3 transition metal-complexes and a Brønsted acid that execute redox-neutral transformations for a series of alkenes, (protected) unsaturated alcohols, and aryl boronic acids, with no or with minimal
intermediary work-up, to furnish varied SBAs in high stereoselectivity, with up to 99:1 er, dr > 20:1, and 91% yield (Fig. 1f-h). We showed that not only the protocols are operationally simpler and up to ~3-fold less resource-intensive than the stepwise synthesis, but also that the overall yield of the product is increased (77% versus 43%) thanks to preventing cumulative losses of the materials during subsequent isolations and purifications of the intermediates.

We initiated the study by validating the possibility to conduct in situ both the isomerization of unsaturated alcohols and the addition of aryl boronic acids to aldehyde intermediates. Model substrates, trans-2-hexenol 1a and phenylboronic acid 2a, reacted to furnish racemic alcohol 3aa, 1-phenyl-1-hexanol in 84% yield in the presence of [Ir(cod)Cl]2 (Ir-1) and [Rh(cod)(CH3CN)2]2(BF4)2 (Rh-1) (Figure 2a). The control experiments confirmed the role of both complexes. The reactivity was diminished when either complex was not present.

Figure 1. Context and the current study: stereoselective synthesis of secondary benzylic alcohols (SBAs).

The enantioselective variant of the transformation required to exchange the Rh-catalyst for the Ru-complex bearing chiral Me-BIPAM, (Ru-1, Figure 2b); the latter being a privileged ligand developed by Yamamoto and Miyaura for enantioselective Rh- or Ru-catalyzed reactions, including 1,2-addition reactions.20,21 We found that although a Rh-catalyst bearing chiral diene ligand Rh-2/cod proved active, product 3aa was formed in modest enantioselectivity (70:30 er). The evaluation of other Rh-complexes bearing N-sulfinyl chiral sulfur-olefin Rh-2/sulpho or phosphine2 Rh-2/BINAP ligands, did not secure any highly enantioselective protocol. In sharp contrast, the reaction in the presence of Ir-1 and (R,R)-Ru-2,21 furnished product (R)-3aa in high er of 96:4, albeit in a low yield of 23%. The use of other isomerization catalysts14 in place of Ir-1 enabled the formation of (R)-3aa in higher yields. The reaction in the presence of Ru-4 and (R,R)-Ru-1 furnished the product in 55% yield and 96:4 er. Further experiments revealed that the presence of Ru-1 partially inhibits the activity of Ir-1. Fortunately, when 1a was shortly incubated in the presence of 0.125 mol% Ir-1, prior to the addition of 2a and (R,R)-Ru-1, (R)-3aa was formed in 81% yield (78% isolated material) and 96:4 er.
The identified protocol proved applicable to a substantial range of aryl boronic acids and alkenylic alcohols (Figure 3). The reactions of 1a with phenylboronic acid derivatives containing an electron-donating or an electron-withdrawing group in the para- or meta-position of the phenyl ring (2b-2i, 2k-2m) as well as those with a sizeable aryl moiety (2o-2q) formed the product with 92:8 to 99:1 er and up to 86% yield. The reactions for aryl boronic acids bearing either a strongly electron-withdrawing group or steric hindrance in the ortho-position, such as 2j and 2r-2t, respectively, furnished the products in modest yields (up to 31%) and moderate enantioselectivity (<79:21 er), indicating the limitations of the protocol. Heteroaryl derivatives, including dibenzo[b,f]thiophene 2o and 1,3-benzodioxole 2p, reacted to form the products in 95:5 er and 33-60% yields. Alcohols containing a remote double bond, such as homoallylic 3-hexenol 1b and 5-hexenol 1c, are suitable substrates; however, the Zipper catalyst Ru-3 was used in place of Ir-1 to form the products in high yields (93% and 90%, respectively). It is worth noting that the presence of Ru-3 bearing an achiral phosphine ligand does not erode the enantioselectivity of the step executed by Ru-1 (96:4 er), demonstrating the key compatibility between the catalysts.

Figure 2. Studies toward enantioselective conversion of allylic alcohols to SBAs. * 1a and Ir-1 was kept at 30 °C for 2 h, followed by the addition of 2a and (R,R)-Ru-1 (6.0 mol%), and kept at 60 °C for 6 h. 2 0.125 mol% Ir-1. 3 Yield of isolated material.

Because cross-metathesis represents a convenient method to install an alkenylic alcohol moiety on olefins, we next sought a protocol that would enable the direct assembly of a SBA from an alkene, a simple alkenylic alcohol, and an aryl boronic acid. Such a method would be attractive due to the increase in the structural diversity of the products, by using combinations of readily accessible
building blocks. However, the requirement of the compatibility of 3 transition-metal catalysts in the series of 3 subsequent processes represents a challenge. Cross-inhibition issues aside, any ligand exchange processes between a metathesis or an isomerization catalyst and a chiral catalyst that operates in the final 1,2-addition step are likely to deteriorate the stereoselectivity.

Figure 3. Scope for conversion of linear alkenylic alcohols to SBAs. a Reagents added to the mixture subsequently without any work-up; yields of isolated material are reported (yields determined by NMR analysis are ~2-13% higher, see the SI); er calculated by SFC analysis. b The 2nd step at 90 °C for 24 h. c Yields by NMR analysis using an internal standard. d Ru-2 (2 mol%).

Initial experiments indicated that a cross-metathesis reaction of alkene 4a and cis-2-butene-1,4-diol (5) in the presence of the o-tolyl Hoveyda-Grubbs Catalyst® M721(Ru-5) followed in situ by the isomerization-addition sequence with 2a, Ru-2, and (R,R)-Ru-1 furnished benzylic alcohol (R)-6aa in 98:2 er (Figure 4). High stereoselectivity of the reaction confirmed the critical compatibility of chiral Ru-1 with the other catalysts in the sequence. However, because of the limited conversion of alkene 4a to allylic alcohol intermediate 7, product (R)-6aa was formed in only up to 11% yield (Tables S1-S2 in the SI). Alkene 4a reacted more readily with 5’, TMS-protected 5, in the presence of Ru-5, forming 7’ in a high yield (>95% by GC analysis). The latter was quickly and quantitatively deprotected to form alkenol 7 in the presence of trifluoroacetic acid. The acid was washed off with an aqueous base solution, and no further workup is required for the subsequent isomerization-addition sequence. However, because the full removal of aqueous phase is essential, we noticed that drying the reaction mixture over Na2SO4 (and its removal) prior the subsequent steps is beneficial for the reproducibility. Overall, such a protocol that engages 3 different Ru-catalysts and a Brønsted acid with a minimal intermediary work-up converts 4a, 5’, and 2a to alcohol (R)-6aa in 88% yield (79% isolated material) and 98:2 er.
Figure 4. Enantioselective sequential multicatalysis for conversion of alkenes to SBAs. a As in Figure 3; no work-up except for washing off TFA and optional drying over Na$_2$SO$_4$; b With cis-2-butene-1,4-diol.

The side-by-side experiments on a 2.4 mmol scale of 4a for the synthesis of (R)-6aa proved that not only is the established protocol faster, more operationally simple, and ~3-fold less resource-intensive than the stepwise approach, but the final yield of the isolated material is also increased, i.e., 77% versus 43%, respectively. Although the consecutive steps of the sequence occurred with similar GC yields in both cases, the sequential protocol prevented cumulative losses of the material during subsequent isolations and purifications of the intermediates, illustrating an additional advantage of the approach (for details, see Tables S3-S4 in the SI).

The established protocol integrating alkene cross-metathesis, isomerization, and enantioselective addition is broadly applicable (Figure 4). A series of aliphatic alkenes, electron-rich or electron-deficient vinyl arenes, TMS-protected alkenol, and stereoelectronically varied aryl boronic acids reacted to form a range of SBAs in high enantioselectivities (er’s > 95:5) and 48-87% yields (isolated material).

Lastly, we focused on allylic alcohols bearing a prochiral double bond. The isomerization-addition sequence for 3-substituted allylic alcohols constitutes an attractive strategy to produce the SBAs bearing two stereocenters with a 1,3-relationship. We surmised that a method utilizing two different chiral catalysts that independently construct each stereogenic center would give access to all 1,3-syn and 1,3-anti stereoisomers of the product. However, the key requirement is the independent activity of both chiral catalysts and their compatibility.
Figure 5. Stereoselective conversion of substitute allylic alcohols to SBAs. As in Figure 2; no workup except for removal of EtOH under vacuum; yields of the isolated major diastereomer. b dr of 1,3-syn (major):1,3-syn(minor):sum of 1,3-anti products.

Combining suitable enantiomers of Ru-3, the isomerization catalyst reported by Ohkuma, and Ru-1 enables the isomerization-addition sequence to form different diastereomers of the products with high stereocontrol in a one-pot fashion (Figure 5). The catalysts proved to require different solvents to operate efficiently (i.e., ethanol and toluene, respectively; for details, see Figures S1-S4, Table S5). Therefore, the medium needs to be exchanged between the steps (evaporation under vacuum); albeit no resource-intensive work-up is needed. Importantly, the stereocontrol for the formation of each stereogenic center is solely determined by the catalyst involved. For instance, while the reaction of geraniol 8a and 2a in the presence of (S)-Ru-3 and (S,S)-Ru-1 furnished 1,3-syn benzylic alcohol (1S,3R)-9aa with >99:1 er, >20:1 dr, in 62% yield, the same reaction but with (R,R)-Ru-1 in place of (S,S)-Ru-1 furnished 1,3-anti diastereomeric alcohol (1S,3S)-9aa', in similarly high 99:1 er, >20:1 dr, and 61% yield. The diastereoselectivity of the transformation depends on the configuration of the double bond in the starting material. Under the conditions that geraniol 8a reacted to form 1,3-syn 9aa, nerol 8b, the (Z)-analogue of geraniol 8a, reacted to form 1,3-anti 9ba' containing the opposite major enantiomer of 9aa', in 99:1 er, >20:1 dr, and 60% yield. Noteworthy, the isolated double bonds of starting materials 8a-8b remained intact in the corresponding products. Chiral phytol 8c, reacted with varied arylboronic acids to form the products in high stereoselectivity, i.e., 90-97% of the major stereoisomer, and from 43% to 70% yield. The presence of an additional chiral center next to the allylic alcohol moiety in the starting material seems not to disturb the reaction. (+)-Limonene derivative 8d reacted with 2a to form 9da in >20:1 dr, and 41% yield, expanding the scope of the system.
In conclusion, the herein disclosed methods enable the rapid modular stereoselective syntheses of a broad range of secondary benzylic alcohols from simple available starting materials. The strategy relies on the construction of the sequences of multiple catalytic reactions occurring consecutively with no or minimal intermediary workup. A transformation is executed with the aid of up to 3 transition metal catalysts and requires a single isolation and purification of the product. Overall, the approach simplifies the synthesis of target motifs, increases material efficiency, and limits cost, time, and waste associated with the standard stepwise procedures. In a greater perspective, the study highlights the synthetic potential of the multicatalytic approaches to access increasingly complex architectures from simple starting materials.

ASSOCIATED CONTENT
Supporting Information. Experimental details and data. This material is available free of charge via the Internet at http://pubs.acs.org

AUTHOR INFORMATION

Corresponding Author
* E-mail: dydio@unistra.fr

Author Contributions
†AC and DL contributed equally.

ACKNOWLEDGMENT

We acknowledge funding from the European Research Council (ERC StG no 804106), the French National Research Agency (ANR IdEx, ANR LabEx „Chemistry of Complex Systems“, and a PhD fellowship for BL under contract 17-EURE-0016). We are thankful to K. Hurej (University of Strasbourg) for preliminary experiments, and D. Leboeuf (University of Strasbourg) for the comments on the manuscript.

DEDICATION

The authors dedicate the paper to Prof. Janusz Jurczak (Polish Academy of Sciences) on the occasion of his 80th birthday.

REFERENCES


