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Remote Functionalization of α,β-Unsaturated Carbonyls by Multimetallic Sequential Catalysis

Ciro Romano, Daniele Fiorito, Clément Mazet*

† Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva, Switzerland.

ABSTRACT: The remote functionalization of α,β-unsaturated carbonyls by an array of multimetallic sequential catalytic systems is described. The reactions are triggered by hydrometallation using [Pd–H] or [Ru–H] isomerization catalysts and driven by the formation of thermodynamically more stable 1,2-vinyl arenes. The Pd-catalyzed deconjugative isomerization was combined with a Cu-catalyzed β-borylation of the transiently generated styrenyl derivatives to deliver a range of products that would not be accessible with the use of a single catalyst. [Pd/Cu] catalytic systems were also identified for the highly enantioselective α-hydroboration and α-hydroamination of the styrenyl intermediates. Difunctionalization simultaneously at the benzylic and homobenzylic positions was achieved by combining the isomerization process with Sharpless asymmetric dihydroxylation (SAD) using [Pd/Os] or [Ru/Os] couples. Starting from a simple α,β-unsaturated ester, an isomerization/dihydroxylation/lactonization sequence gave access to a naturally occurring γ-butyrolactone in good yield, excellent diastereo- and enantioselectivity.

■ INTRODUCTION

The remote functionalization of an organic molecule consists in interconverting two distant functional groups by a relay process either through (i) space or (ii) across the constitutional skeleton.[1] The former usually requires the elaboration, installation and subsequent removal of often complex directing templates to achieve the desired distant functionalization.[2] The latter is typically accomplished by alkene migration along a hydrocarbon chain and driven by a thermodynamically favorable termination process.[3] This enabling strategy has gained increased momentum over the last few years, leading to the development of particularly innovative transformations (Figure 1, A).[4-8] Two key notions must be taken into consideration for the successful realization of remote functionalization protocols based on alkene migration. First, the *initiation phase*, which depends on: (i) the triggering event that initiates olefin migration; (ii) the extent of substitution of the olefin, a crucial parameter for reactivity. Second, the *driving force* of the process, which includes: (i) the ability of the catalyst to sustain olefin migration along the hydrocarbon chain, independently of its length (favorable kinetics); (ii) the nature of the terminal functional group undergoing refunctionalization (favorable thermodynamic). This last aspect is intimately associated with the nature and thermodynamic stability of the organometallic intermediate which usually precedes product formation. Specifically, metallo-carbinol species such as **A** were found to intervene before reinstallation of the unsaturation in several reactions, including in deconjugative processes (Figure 1, B).[4] A complementary approach consists in intercepting a α-benzyl organometallic (**B**),[5] a primary alkyl organometallic (**C**),[6] or a C-bound metal-enolate (**D**) with an appropriate coupling partner (Figure 1, C-D).[7-8]

The economic and environmental benefits associated with sequential multimetallic catalysis has raised strong interest in academia and industry.[9-11] The field emulates from Nature's ability to separate different reactive sites within an enzyme, or different enzymes within a cell to effect a series of orthogonal transformations in a given sequence without the need to isolate unstable reactive intermediates. The implementation of such strategies in synthetic laboratories may ultimately enable chemists to readily convert commodity chemicals into more complex molecular architectures with maximum efficiency - be it in terms of atom-, step-, redox-economy, absolute and relative stereocontrol.[12] A paramount challenge is to meet the requirement for time resolution and compatibility of all reagents and catalysts to a single set of reaction conditions. Recently, the Marek laboratory and our group independently merged the concepts of remote functionalization and multimetallic catalysis with the development of complementary isomerization/cross-coupling sequences using [Ir/Ni], [Pd/Ni] and [Ru/Ni] combinations.[13] These protocols afford highly substituted alkenes from readily available alkenyl methyl ethers via the intermediacy of stereodefined methyl vinyl ethers that would be difficult to access and isolate by conventional methods.

As an extension of this approach, we hypothesized that, if judiciously designed, remote functionalization by sequential multimetallic catalysis may enable (i) to react the intermediates resulting from alkene isomerization at positions that are not imposed by the thermodynamically favored organometallic species generated upon chain-walking, and (ii) to further diversify the scope of refunctionalizations by use of a second transition metal. These subsequent orthogonal transformations would not be conceivable with the catalyst used for isomerization (Figure 1, E).

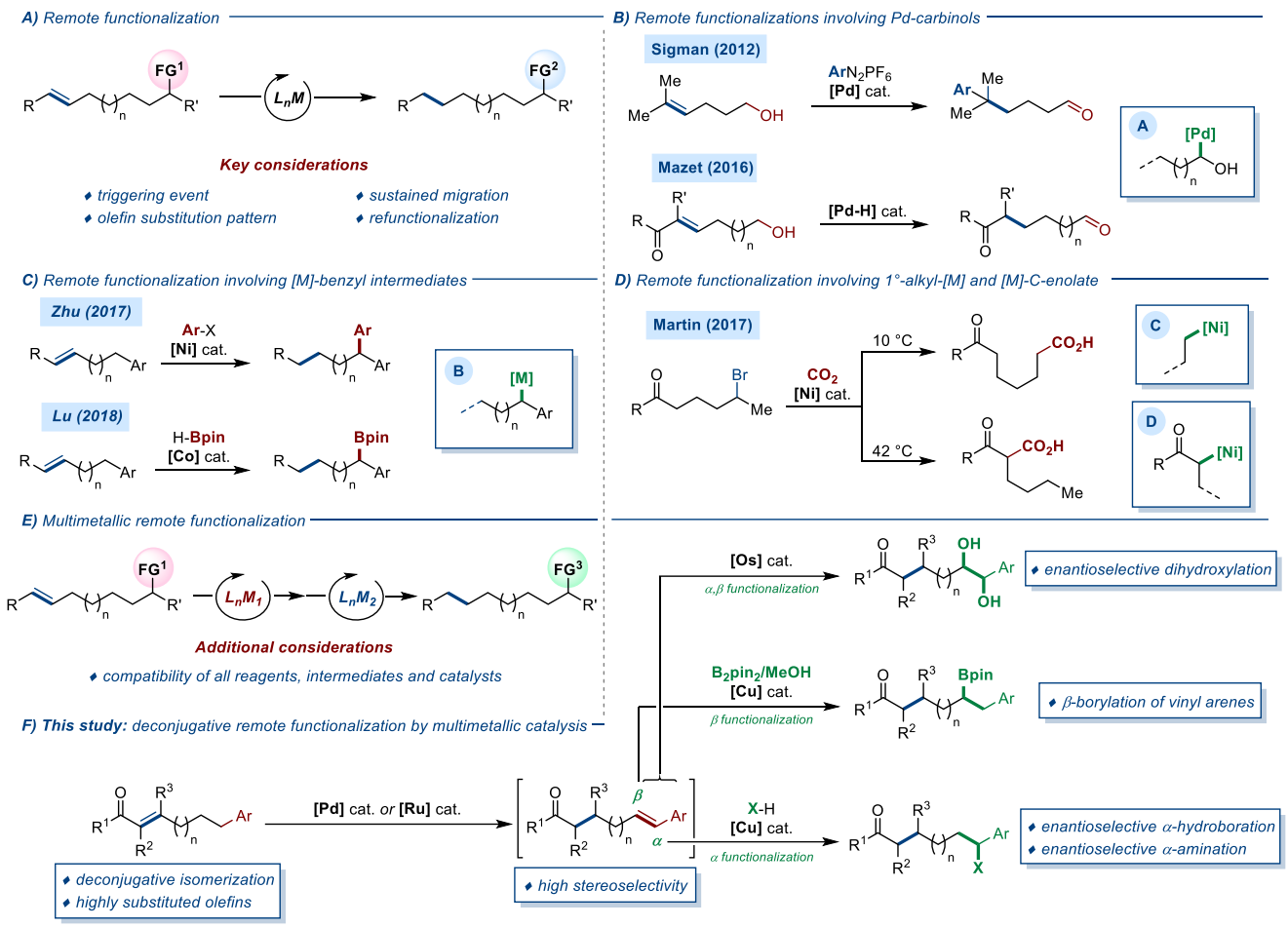


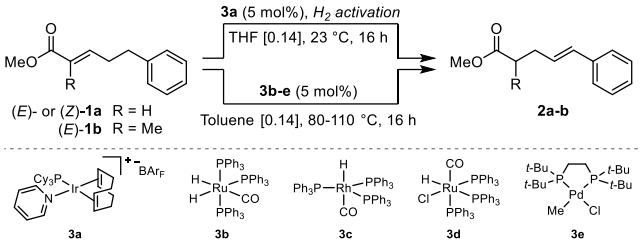
Figure 1. (A) Remote functionalization by transition metal-catalyzed alkene migration. (B) Remote functionalizations involving Pd-carbinol intermediates. (C) Remote functionalizations involving transition metal-benzyl intermediates. (D) Remote functionalizations involving primary alkyl transition metal intermediates and transition metal C-enolates. (E) Principle of remote functionalization by sequential multimetallic catalysis. (F) This study: deconjugative remote functionalizations based on the enantioselective α-hydrofunctionalization, β-borylation and asymmetric dihydroxylation of the transiently generated 1,2-vinyl arenes using [Pd/Cu], [Ru/Os], [Pd/Os] catalytic sequences.

Herein we report the validation of this approach with the devise of several multimetallic sequences initiated by the long-range deconjugative isomerization of α,β-unsaturated carbonyls catalyzed by either a ruthenium or a palladium complex and driven by the formation of a remote vinylarene. These intermediates were typically generated with high levels of stereoselectivity and engaged in a subsequent functionalization in the same reaction vessel. First, a challenging Cu-catalyzed borylation at the homobenzylic position was achieved for a variety of derivatives providing access to multifunctional scaffolds that could not be prepared with a single transition metal catalyst. Next, conditions compatible with Cu-catalyzed enantioselective α-hydroboration and enantioselective α-amination reactions were identified when a Pd catalyst was used for the deconjugative process. Finally, a [Ru/Os] catalytic combination enabled highly selective dihydroxylation of the in situ generated vinylarene. The possibility to increase molecular complexity using this strategy was established in an isomerization/dihydroxylation/lactonisation sequence providing access to a naturally occurring γ-butyrolactone.

■ RESULTS AND DISCUSSION

We have previously established that the refunctionalization of an alcohol into a ketone or an aldehyde constitutes a sufficiently strong driving-force to effect the deconjugative isomerization of α,β-unsaturated carbonyls by palladium catalysis.[4k] We decided to explore the possibility to extend this process to substrates terminated by an aromatic ring to access the corresponding vinylarenes by investigating the isomerization of the α,β-unsaturated ester (*E*)-**1a** with a selection of well-established isomerization catalysts **3a-e** (Table 1). Satisfactorily, product formation was observed in all cases. Only moderate conversion into styrenyl **2a** were achieved with the Pfaltz modified version of Crabtree catalyst **3a** activated by H_2 and with $[(Ph_3P)_3Ru(H)_2(CO)]$ **3b** (Entry 1-2).[14] With the neutral rhodium hydride complex $[(Ph_3P)_3RhH(CO)]$ **3c**, conversion into **2a** was also incomplete. Nearly 16% of a 4:1 *E*/*Z* mixture of the intermediate internal alkenes was observed. The ruthenium monohydride $[(Ph_3P)_3RuH(CO)(Cl)]$ **3d** and our home-made palladium precatalyst **3e** afforded **2a** in 92%

Table 1. Catalyst identification[a]



Entry	Substrate	Catalyst	Conv. (%)[b]	*E*/*Z* **2**[b]
1	(*E*)-**1a**	**3a**	46	>20:1
2	(*E*)-**1a**	**3b**	52	>20:1
3	(*E*)-**1a**	**3c**	31	>20:1
4	(*E*)-**1a**	**3d**	92	>20:1
5	(*E*)-**1a**	**3e**[c]	94	>20:1
6	(*E*)-**1b**	**3d**	58	>20:1
7	(*E*)-**1b**	**3e**[c]	88	>20:1
8	(*Z*)-**1a**	**3e**[c]	93	>20:1
9	(*E*)-**2a**	**3d**	8	>20:1
10	(*E*)-**2a**	**3e**[c]	6	>20:1

[a] 0.15 mmol scale. [b] Determined by ^{1}H NMR using an internal standard. [c] **3e** activated using 5.5 mol% of $NaBAr_F$.

and 94% conversion with very high levels of stereocontrol (*E*/*Z* >20:1) (Entry 3-5). Only partial conversion was achieved for the deconjugative isomerization of the sterically more demanding α-substituted α,β-unsaturated ester (*E*)-**1b** using the ruthenium precatalyst **3d**. With the palladium complex **3e**, the styrenyl derivative **2b** was generated in 88% and *E*/*Z* >20:1 (Entry 6-7). Isomerization of (*Z*)-**1a** afforded (*E*)-**2a** with excellent stereoselectivity, highlighting the stereoconvergent nature of the isomerization process (Entry 8). Both for **1a** and **1b**, despite the excellent catalytic efficiency observed with **3d** and **3e**, physical separation of the styrenyl product from the substrate could not be achieved. Attempts to reach complete conversion by systematic variation of the reaction parameters (catalyst loading, reaction time, temperature…) were not met with success, thus severely limiting the practicality of the process. When **2a** (prepared by an independent route) was subjected to the optimized catalytic conditions using either **3d** or **3e**, formation of the α,β-unsaturated ester was observed in 8% and 6% respectively (Entry 9-10). These results indicate that the isomerization reaction is reversible and under thermodynamic control, with preference for the formation of the styrenyl derivatives **2** when **3d** and **3e** are employed.

In line with our initial objectives, we subsequently sought to identify a catalytic transformation for the *in situ* β-functionalization of the styrenyl derivatives obtained upon deconjugative isomerization. Ultimately, this would not only allow us to potentially circumvent purification issues but, more importantly, to functionalize the products of isomerization at a less conventional position while increasing molecular complexity. *The catalytic and site-selective β-functionalization of 1,2-vinylarenes constitute a contemporary challenge in itself and the number of successful examples of such processes remains quite limited.* Due to the robustness of the reaction conditions, we reasoned that the Cu-catalyzed β-borylation of 1,2-vinylarenes pioneered by Hoveyda may constitute a suitable entry point for the development of a multimetallic sequence.[15] Upon testing this hypothesis, we were pleased to find that the two catalytic systems were compatible. Indeed, only marginal adjustment of the original reaction conditions of the protoboration were necessary to perform sequentially, in the same reaction vessel, and without solvent switch, the Pd-catalyzed deconjugative isomerization of **1a** and the Cu-catalyzed β-selective functionalization of the transiently generated vinyl arene **2a**. Gratifyingly, using [(IMes)CuCl], NaOtBu, B_2pin_2 and MeOH at room temperature in the second part of the sequence, the final borylated product **3a** could be isolated in pure form in 73% yield after purification by column chromatography and separation from the product of conjugate addition to **1a** (Figure 2). Formation of the product of α-borylation was not observed.

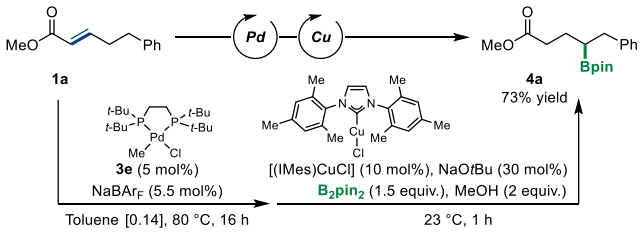


Figure 2. Remote functionalization of **1a** by a [Pd/Cu]-catalyzed deconjugative isomerization/β-borylation sequence.

The generality of this sequential multimetallic catalytic process was explored using the optimized conditions (Figure 3). To fully appreciate the combined efficiency of the two catalysts when operating in sequence, Figure 3 also contains the ratio between the α,β-unsaturated carbonyl and the vinyl arene measured when the Pd-catalyzed deconjugative isomerization reaction is performed independently. In most cases, variation of the terminal aromatic ring had only a limited impact on the ratio between the α,β-unsaturated ester and the vinyl arene remained very high, ranging from 7:93 to 1:99 (**2a,c-h**). All styrenyl products were obtained with excellent stereoselectivity (*E*/*Z* >20:1). The furan and Boc-indole derivatives (**1i,j**) led to much reduced chemoselectivity (21:79 and 40:60 respectively), and **2j** was generated with decreased stereoselectivity (*E*/*Z* = 7.2:1). When these reactions were run in sequence, the borylation products were isolated in moderate to high yields. Starting from **1b**, the product of β-borylation **4b** was isolated in 79% (*dr* 1:1) after conducting the [Pd/Cu] catalytic sequence. In contrast, the presence of a β-substituent on the α,β-unsaturated ester drastically affected the efficiency of the isomerization process and consequently the yield of the Cu-catalyzed borylation reaction (**4k**: 37%, *dr* 1.7:1). Isomerization of **1l** to generate the styrenyl derivative **2l**, featuring a trisubstituted alkene, was quantitative.

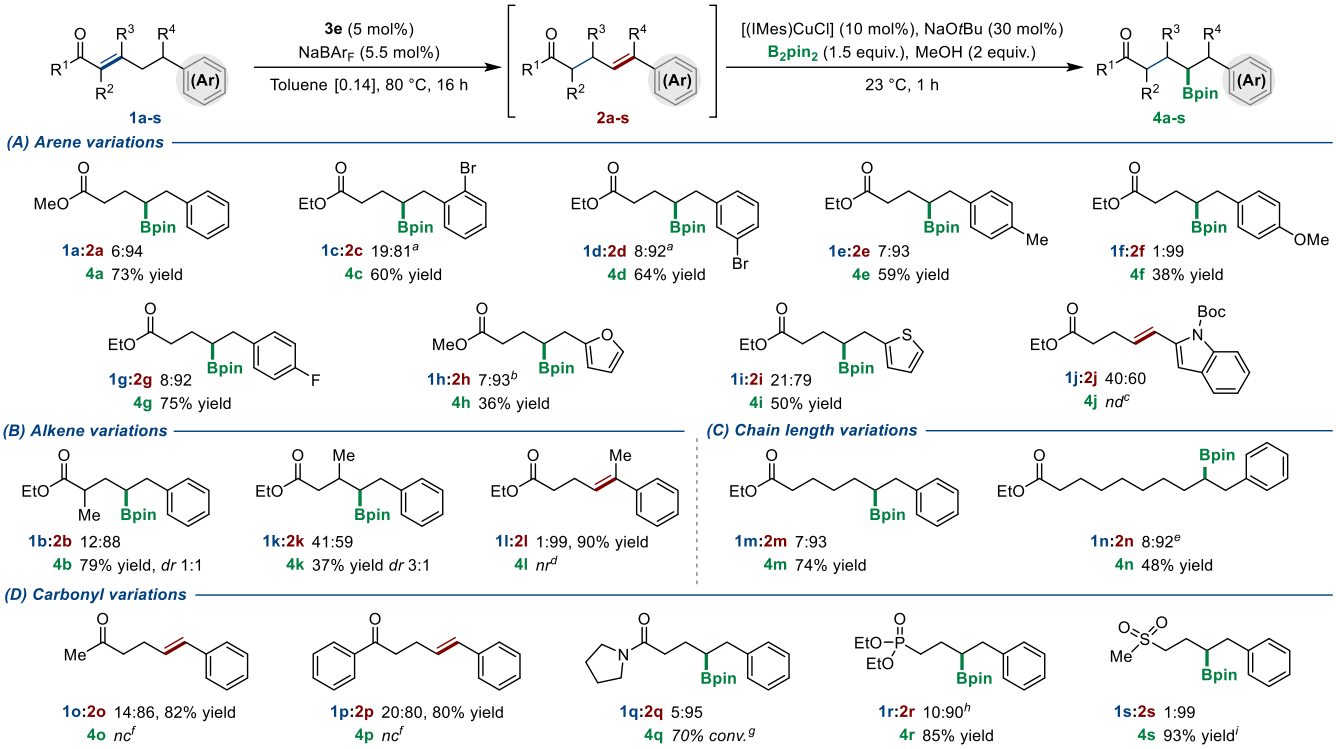


Figure 3. Scope of the Pd-catalyzed deconjugative isomerization of α,β-unsaturated carbonyls and scope for the [Pd/Cu]-catalyzed deconjugative isomerization/β-borylation sequence. The **1:2** ratio was determined by ^{1}H NMR using an internal standard. Reactions performed on a 0.2 mmol scale. (A) Variations of the arene end-group. (B) Variations of the alkene substitution pattern. (C) Effect of chain length on catalytic efficiency. (D) Variation of the carbonyl head group. [a] Isomerization run at 60 °C for 24 h. [b] Isomerization run at 120 °C for 18 h. [c] Not determined. [d] No reaction. [e] Contains ca. 40% of internal olefins. [f] Not compatible. [g] 1:2.3 mixture of **2q** and **4q**. [h] Contains ca. 5% of internal olefins. [i] Using 1.1 equiv. of B_2pin_2.

Consistent with literature precedents, Cu-borylation of the congested C=C bond was ineffective. We established that the Pd-catalyzed deconjugative isomerization is essentially insensitive to the chain length between the carbonyl function and the remote aryl group, and could perform the remote borylation of **1m** and **1n** with selectivity similar to that of the model substrate (7:93 and 8:92 respectively; **4m**: 74% yield; **4n**: 48% yield after purification). Nonetheless, in the case of the 9-C atom substrate **1n**, nearly 40% of internal olefin isomers were observed after the isomerization step. Finally, we found that α,β-unsaturated alkyl ketone (**1o**), aryl ketone (**1p**), tertiary amide (**1q**), phosphate (**1r**) and sulfone (**1s**) are all competent functional groups in the deconjugative isomerization, affording the corresponding vinyl arenes with good to excellent **1:2** ratios. Even though the ketone derivatives are not compatible with the reaction conditions for borylation, we were able to isolate the products of isomerization in high yield (**2o**: 82%; **1p**: 80%). Even when the stoichiometry and catalyst loading were adjusted, only partial borylation was achieved with the amide derivative **4q**, leading to an intractable mixture of isomerization and borylation products. Satisfactorily, **4r** and **4s**, the products of the deconjugative isomerization/borylation sequence of the corresponding α,β-unsaturated phosphate and sulfone were obtained in high yield (85% and 75% respectively).

As a following challenge, we decided to investigate whether the Pd-deconjugative isomerization could be combined with enantioselective hydrofunctionalizations of the vinyl arenes generated in situ.[16] Not only are these reactions particularly sensitive to subtle changes in the experimental conditions, but the association of two metal-hydride catalysts may constitute an additional hurdle to the successful development of such multimetallic sequences.

The enantioselective α-hydroboration of 1,2-substituted vinyl arenes that produces benzylic boronic esters finds limited precedents in the literature.[17] We initiated our investigations by testing the optimum system described by Yun and coworkers for the Cu-catalyzed hydroboration of β-methyl styrene[17a] on the independently prepared styrenyl derivative **2a** and were pleased to isolate the targeted benzyl boronate **5a** in 57% yield and 95% *ee* (as compared to 71%, 95% *ee* for the product of β-methyl styrene) (Figure 4, A). The remote functionalization of **1a** performed by applying the Pd-catalyzed isomerization/Cu-catalyzed hydroboration sequence in one-pot afforded **5a** in only 48% yield and with a much reduced enantioselectivity (86% *ee*) (Figure 4, B). Several chelating bis-phosphine ligands were evaluated using the conditions for sequential catalysis (See Supporting Information). Gratifyingly, another P-stereogenic ligand, BenzP* (**L$_2$**) delivered **5a** in low yield but with excellent enantioselectivity (27% yield, 97%).

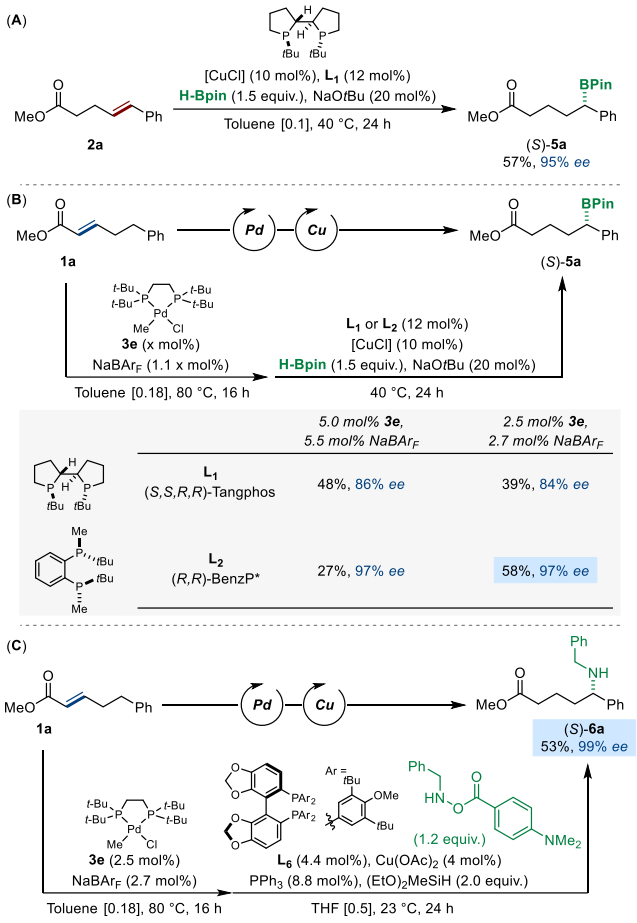


Figure 4. (A) Cu-catalyzed enantioselective α-hydroboration of **2a**. (B) Sequential [Pd/Cu]-catalyzed deconjugative isomerization/α-hydroboration of **1a**. Effect of relative catalyst loading. (C) Remote functionalization of **1n** by a [Pd/Cu]-catalyzed deconjugative isomerization/α-hydroboration sequence. (D) [Pd/Cu]-catalyzed deconjugative isomerization/α-hydroamination of **1a**.

When the catalyst loading in **3e** was halved to minimize potential interactions between the in situ generated [Pd–H] catalyst and the Cu catalyst, a reduced reactivity was observed with L_1 but, remarkably, boronate **5a** could be isolated in 58% yield and 97% *ee* with L_2.

A similar approach was followed for the development of Pd-catalyzed deconjugative isomerization/Cu-catalyzed enantioselective hydroamination sequence (Figure 4, C). Using the protocol developed by Buchwald and co-workers as starting point,[18] we found that best performances were achieved when the loading in **3e** was reduced. This is presumably due to minimized detrimental interaction between both transition metal catalysts. Moreover, to be fully operative, the system required to switch solvent from toluene to THF after the isomerization reaction. The Cu-catalyzed hydroamination was therefore conducted on the crude reaction mixture resulting from deconjugative isomerization of **1a** using diethoxymethylsilane, benzylamino-4-(dimethylamino)benzoate as the amine transfer reagent and (*R*)-DTBM-Segphos L_6 as chiral ligand to afford the product of remote functionalization **6a** in 53% yield and 99% *ee*.

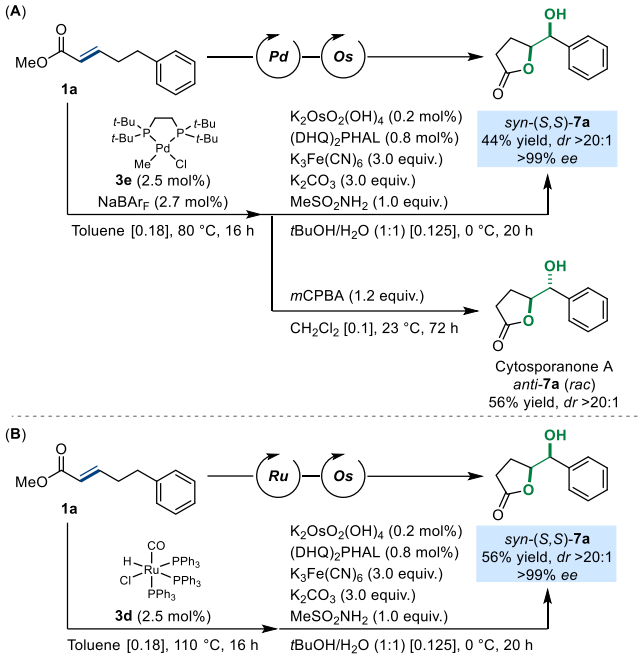


Figure 5. (A) Enantioselective access to γ-butyrolactone **7a** by a [Pd/Os]-catalyzed deconjugative isomerization/SAD/lactonization sequence. (B) Enantioselective access to γ-butyrolactone **7a** by a [Ru/Os]-catalyzed deconjugative isomerization/SAD/lactonization sequence. (C) Remote functionalization of **1n** by a [Ru/Os]-catalyzed deconjugative isomerization/SAD sequence.

To further demonstrate the potential of remote functionalization strategies by sequential multimetallic catalysis, we turned our attention to the Sharpless asymmetric dihydroxylation of alkenes (SAD),[19] a protocol that could potentially allow to orthogonally functionalize the in situ generated 1,2-vinyl arenes both at the benzylic and homobenzylic positions. The mechanism of the SAD has been extensively studied and is relatively well understood. A less enantioselective secondary cycle in which the osmium catalyst is not bound to the chiral ligand has been identified. We anticipated that if any perturbation of the chiral osmium catalyst during the isomerization/SAD sequence (e.g. ligand exchange) might increase the contribution of the secondary cycle and, consequently, deplete the enantiomeric excess of the product. To test the viability of the [Pd/Os]-catalytic combination, our model substrate **1a** was subjected to deconjugative isomerization using 2.5 mol% of **3e** and subsequently to the prototypical reaction conditions for SAD using AD-mix-α (0.2 mol% in [Os]). Pleasingly, not only both protocols were found to be compatible, but a lactonization between the methyl ester and the newly generated homobenzylic alcohol delivered *syn*-(*S,S*)-**7a** in 44% yield, *dr* >20:1 and >99% *ee* (Figure 5, A). Interestingly, γ-butyrolactone *syn*-(*S,S*)-**7a** is a naturally occurring product originating from sponge-derived fungi, which was found to display anti-nematodal activity.[20] Substituting AD-mix-α by *m*CPBA in the second part of the sequence provided access to another natural product isolated from fungi which displays antimicrobial activity: Cytosporanone A (*anti*-**7a**: 56% yield and *dr* >20:1).[21] In contrast to

the previous multimetallic sequences, we found that [[$(Ph_3P)_3$RuH(CO)(Cl)] **3d** (2.5 mol%) could be successfully associated with the osmium catalyst to afford *syn*-(*S,S*)-7a in an improved 56% yield while maintaining similar selectivity (*dr* 20:1 and >99% *ee*) (Figure 5, B). Overall, this sequence consisting of a deconjugative isomerization, an enantioselective dihydroxylation and a lactonization enabled to substantially increase the level of molecular complexity from a simple α,β-unsaturated ester to a biologically active natural product. This result underscores the potential of remote functionalization by multimetallic catalysis.

In summary, we have developed a series of remote functionalizations based on sequential multimetallic catalytic reaction performed in a single reaction vessel. These sequences are initiated by Pd- or a Ru-catalyzed deconjugative isomerizations of α,β-unsaturated carbonyl compounds. Although reversible, the isomerization is under thermodynamic control and driven by the formation of the more stable styrenyl derivatives. Consistent with previous observations from our laboratory, the palladium complex was found to be less sensitive to higher steric demand from the olefinic substrate. Therefore, the scope of the Pd-catalyzed deconjugative isomerization was investigated in details and successfully combined with a Cu-catalyzed β-borylation of the transiently generated 1,2-vinyl arenes. Each elementary reaction is challenging when considered independently and remote functionalization at the homobenzylic position would not be conceivable with the exclusive use of known isomerization catalysts. The sequence was found to be compatible with a variety of carbonyl derivatives, several sensitive functional groups and to tolerate various olefinic substitution patterns. Two isomerization/enantioselective α-hydrofunctionalization sequences using [Pd/Cu] combinations have also been developed. We demonstrated that the combination of the isomerization system with established protocols is not necessarily straightforward. Aside from the identification of a suitable chiral ligand, we showed that adjustment of the relative catalyst loadings is crucial to reach satisfactory reactivity and attain excellent enantioselectivity levels. Products resulting from formal remote α-hydroboration and α-hydroamination were thus obtained in practical yield and very high *ee*. Finally, a naturally occurring γ-butyrolactone with anti-nematodal activity was accessed in enantiopure form starting from a simple α,β-unsaturated ester by effecting a sequence of three consecutive events consisting in an isomerization, an asymmetric dihydroxylation and a final lactonization. The [Ru/Os] catalytic combination proved slightly superior to the [Pd/Os] couple.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization of all new compounds and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Prof. Clément Mazet. University of Geneva, Organic Chemistry Department. Quai Ernest Ansermet 30, Geneva 1211 - Switzerland. clement.mazet@unige.ch

Notes

The authors declare no competing financial interests.

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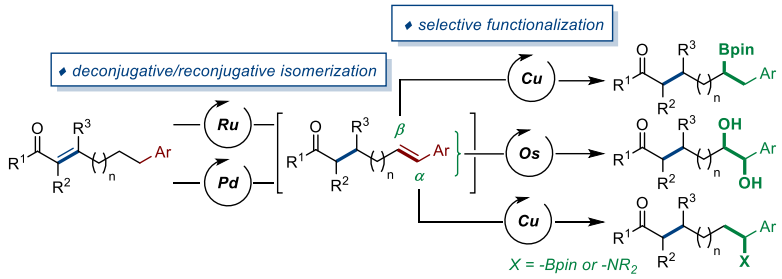
selective functionalization
deconjugative/reconjugative isomerization
Ru
Pd
Cu
Os
Cu
Bpin
OH
OH
X = -Bpin or -NR2