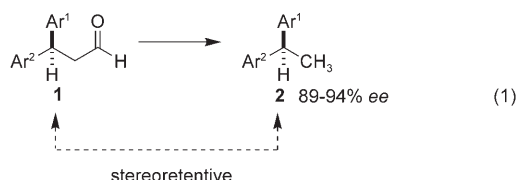


Enantioselective Preparation of 1,1-Diarylethanes: Aldehydes as Removable Steering Groups for Asymmetric Synthesis**

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Among the varied contributions that asymmetric synthesis can make to the drug-discovery process and materials research, access to collections of novel, diverse chemical entities is eminent.^[1] This enabling feature facilitates entry into uncharted chemical and intellectual property (IP) space. In this context, the demand for optically active building blocks continues to rapidly expand. Herein, we document the preparation of optically active 1,1-diarylethanes from β,β -diarylpropionaldehydes [Eq. (1)]. We describe convenient procedures for the decarbonylation reaction ($\text{RCHO} \rightarrow \text{RH}$)



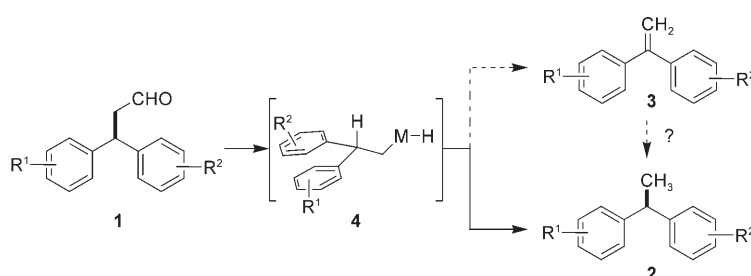
of substrates incorporating functionalities relevant to the synthesis of complex molecules. Additionally, an enantioselective, sequential 1,4-addition/decarbonylation procedure furnishes a one-pot route to 1,1-diarylethanes. More broadly, the work entails the implementation of a new strategy for asymmetric synthesis, involving the use of aldehydes as removable steering groups.^[2]

To date, optically active diarylalkanes can be prepared through some rather laborious approaches.^[3] These include asymmetric alkylations of lithiated diarylmethanes,^[4] and Pd-catalyzed cross-couplings of benzylsilanes with aryl triflates.^[5] The former procedure is limited in scope and suffers from modest yields. The cross-coupling approach requires the synthesis of benzylsilane precursors in optically active form, which is not trivial.^[6] There has been significant progress in enantioselective $\text{C}=\text{C}$ reductions,^[7] yet

the approaches rely on steric or electronic biasing of the flanking substituents of an olefin to obtain asymmetric induction. Consequently, it is hardly surprising that enantioselective hydrogenation of 1,1-diarylethenes lacks precedence.

We have previously reported the catalytic enantioselective 1,4-addition of arylboronic acids to cinnamaldehyde derivatives with rhodium–diene complexes^[8] to generate β,β -diarylpropionaldehydes **1** in high enantiopurity.^[9] The use of **1** as a building block can be envisioned to involve common synthetic steps, such as condensations, additions, reductive aminations, and olefination reactions, all of which enjoy significant precedence. With a view to expanding the menu of transformations available to **1**, we have examined these aldehydes as substrates for the catalytic decarbonylation reaction.

At the outset, it was not obvious whether the decarbonylation reaction of β,β -disubstituted aldehydes **1** could be successfully implemented as an enantioselective approach to 1,1-diarylethanes (Scheme 1). It was also not clear whether the reaction itself would be relevant in the formation of the



Scheme 1. Metal-mediated decarbonylation versus dehydroformylation.

desired optically active products and whether the formation of the corresponding unsaturated by-products **3** would lead to complications. Thus, for example, in preliminary experiments with Rh, Pd,^[10] and Ir^[11] catalysts, competitive formation of the 1,1-diarylethene **3** was observed. It is likely that **3** arises following β -hydride elimination by intermediate **4**. The formation of **3** could have deleterious consequences because subsequent reduction would lead to erosion in the optical purity of **2**.

To examine the use of the decarbonylation of β,β -disubstituted aldehydes as an approach to 1,1-diarylethanes, we screened a range of conditions with aldehyde **1a** ($\text{Ar}^1 = \text{Ph}$, $\text{Ar}^2 = p\text{-(MeO)C}_6\text{H}_4$) as a test substrate. The standard procedure for this reaction prescribes the use of Wilkinson's

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complex, $[\text{RhCl}(\text{PPh}_3)_3]$, in stoichiometric quantities.^[12] This follows because the intermediate Rh–CO species generated in the course of the reaction is stable (up to 200 °C) and incapable of engaging in further decarbonylations. In the case of **1a**, stoichiometric quantities of Wilkinson's complex in toluene at 110 °C furnished the corresponding product (**2a**) in 90% yield along with 4% of the corresponding ethene derivative.

A number of methods have been devised to regenerate the active decarbonylating Rh species in situ.^[13] For example, reactions have been carried out with catalytic amounts of Rh at $\geq 200^\circ\text{C}$ to remove CO or with additives such as diphenylphosphoryl azide (DPPA, typically 1–2 equiv).^[14] For **1a**, the addition of 1.2 equiv DPPA permitted the reaction to be conducted at 50 °C with 10 mol% $[\text{RhCl}(\text{PPh}_3)_3]$, furnishing **2a** in 77% yield. However, we note that rigorous exclusion of moisture is required as well as slow (syringe pump) addition of distilled DPPA. Given the potentially explosive nature of DPPA as well as its hydrolysis product (HN_3), we sought more practical, catalytic decarbonylation methods.

In screening of conditions, 1,3-bis(diphenylphosphino)propane (dppp) proved effective at facilitating decarbonylations with rhodium species.^[15] When the reaction was performed with $[\text{Rh}(\text{dppp})_2\text{Cl}]$ (generated in situ from $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ and dppp; cod = cyclooctadiene) in a sealed tube in refluxing toluene or *m*-xylene, no conversion was observed in the former case and a complex mixture of products in the latter. However, the use of the higher-boiling solvent, *p*-cymene, at 140 °C, with a continuous stream of N_2 to purge the reaction mixture of CO, allowed the isolation of **2a** in 92% yield [Eq. (2)].

With this workable decarbonylation protocol in hand (2 mol% $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$, 8 mol% dppp, *p*-cymene, 140 °C, continuous N_2 stream), we examined the scope of the reaction (Table 1). The optical purity of the products obtained was observed unchanged from that of the starting aldehydes.^[16,17] Numerous functional groups are compatible with the process, including ethers, halides, esters, and nitro groups (Table 1, entries 1–6). Of further interest, substrates containing furans, thiophenes, and indoles are also well tolerated, furnishing decarbonylation products in high yield (Table 1, entries 7–9).

We subsequently set about developing a one-pot protocol, allowing direct conversion of the cinnamaldehyde derivatives into 1,1-diarylethane products without the need to isolate the intermediate aldehydes. The reaction of *trans*-cinnamaldehyde with 4-methoxyphenylboronic acid was conducted with $[\{\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}\}_2]$ and dolefin ligand according to the literature procedure.^[9] When the formation of **1a** was observed to be complete, MeOH was removed in vacuo and replaced by *p*-cymene.^[18] The decarbonylation step was then performed with the same rhodium–diene complex at 140 °C with N_2 sparging. The desired product was isolated in 33% yield from the reaction mixture after 40 h. Although this result is unoptimized, it constitutes, to the best of our knowledge, the first example of decarbonylation of an aldehyde with a rhodium–diene complex, in the absence of phosphine ligand. Additional benefits in yield were observed with added dppp and slightly increased catalyst loading. In the event, following

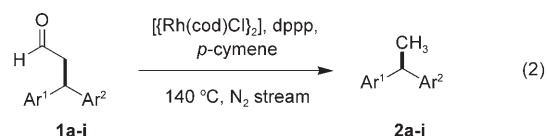
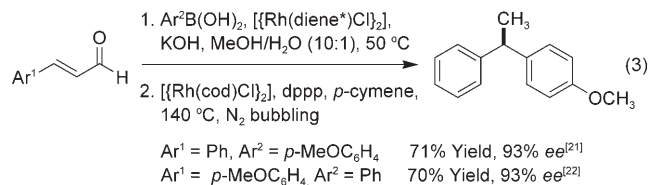


Table 1: 1,1-Diarylethanes prepared from cinnamaldehydes via β,β -diaryl propionaldehydes **1** as intermediates.^[a]

Entry	Aldehyde	Diarylethane	Yield [%]	ee [%] ^[b]
1			92	94
2			89	92
3			96	89
4			97	90
5			90	90
6			92	–
7			83	93
8			89	92
9			98	94

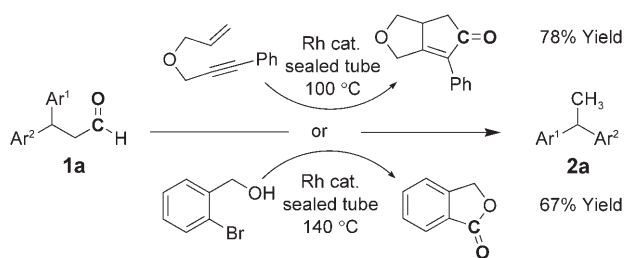
[a] Typical conditions: $[\{\text{Rh}(\text{cod})\text{Cl}\}_2]$ (2 mol%), dppp (8 mol%), *p*-cymene, 140 °C, N_2 stream. [b] For **2a–d** and **2i** the enantiopurity was determined by HPLC and by comparison to authentic racemates. For **2e**, **2g**, and **2h** the enantiopurity could not be assessed by HPLC and was therefore correlated to that of the starting aldehyde by analogy to **2a–d** and **2i**. The enantiomers of **1f** and **2f** could not be separated by HPLC with a chiral phase.

conjugate addition (1.5 mol % $[\text{Rh}(\text{dolefin})\text{Cl}]_2$), addition of 1.5 mol % $[\text{Rh}(\text{cod})\text{Cl}]_2$ along with 3.3 mol % dppp led to **2a** in 71 % yield. Significantly, the optical purity of the diaryl-alkane product was 93 % *ee* [Eq. (3)].



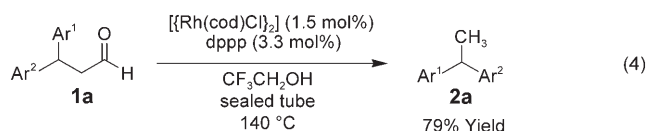
In the course of our investigations, it became clear that under the conditions described above the decarbonylation reaction might prove problematic for small-scale reactions and/or with more volatile aldehydes. Consequently, we examined the possibility of coupling the decarbonylation to a process that consumes CO. This would facilitate turnover and obviate the need to physically remove CO. The coupled reaction would need to consist of substrates, intermediates, and products that do not themselves undergo reaction with aldehydes or inactivate the decarbonylation catalyst.

We became intrigued by two key reports describing aldehydes as sources of CO. In the first of these it had been shown that aldehydes may participate in Pauson–Khand reactions,^[19] and the second involved the carbonylative cyclizations of benzylic alcohols.^[20] These results suggested that coupling of the decarbonylation reaction to either of the carbonylative cyclizations could prove useful for our own objectives. Indeed, the decarbonylation reaction of **1a** could be performed neat in a sealed vessel at 100 °C in the presence of 2 equiv [3-(allyloxy)prop-1-ynyl]benzene (Scheme 2) to furnish **2a** in 78 % yield. Additionally, the decarbonylation of **1a** could be performed with 1 equiv of commercially available *o*-bromobenzylalcohol at 140 °C in a sealed vessel, affording **2a** in 67 % yield.



Scheme 2. Chemical traps for CO lead to catalytic decarbonylation.

During the course of our initial solvent-screening campaign, we had identified yet another procedure to effect the decarbonylation reaction without the need for CO sparging or the use of CO-trapping agents. Interestingly, when the reaction was conducted with 1.5 mol % $[\text{Rh}(\text{cod})\text{Cl}]_2$ and 3.3 mol % dppp in a sealed vessel with $\text{CF}_3\text{CH}_2\text{OH}$ as solvent, **2a** was isolated in 79 % yield [Eq. (4)]. This unusual solvent effect has not, to the best of our knowledge, previously been



observed. It may open up new possibilities for the decarbonylation reaction as a preparatively useful procedure.

In conclusion, we have reported an efficient process to form 1,1-diarylethane compounds in high yield and high optical purity. We have also conducted the transformation using a tandem 1,4-addition of boronic acids to cinnamaldehydes followed by a Tsuji–Wilkinson decarbonylation. It is worth noting that this family of compounds is otherwise not readily accessed enantioselectively by existing methodologies. An additional salient feature of the work is the identification of several protocols with which to effect decarbonylation, including mechanistically intriguing solvent effects. Conceptually, the work described provides a useful strategy for asymmetric synthesis, wherein an aldehyde acts as an activating/directing group and is subsequently removed or excised. When this concept has been used previously the excisable groups have been limited to heteroatom-based systems, such as sulfones or nitroalkanes. The field of enantioselective synthesis has recently witnessed some impressive advances with methods employing unsaturated aldehydes. In this respect, the decarbonylation strategy we describe may have additional useful applications.

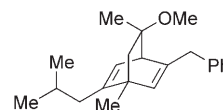
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