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Ruthenium-Catalyzed Aldehyde Functionality Reshuffle: Selective Synthesis of *E*-2-Arylcinnamaldehydes from *E*-β-Bromostyrenes and Aryl Aldehydes

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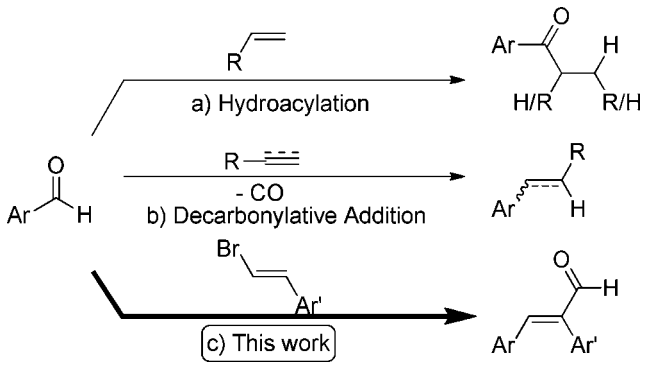
Supporting Information

ABSTRACT: A new concept for highly selective synthesis of *E*-2-arylcinnamaldehydes has been developed via a formal arylformylation of *E*-β-bromostyrenes with readily available aryl aldehydes. This strategy involves an overall reshuffle of the aldehyde functionality with a loss of hydrogen bromide.

An impressive number of classical textbook name reactions rely on the unique reactivity of aldehydes, namely the electrophilic character of the carbonyl group and the generation of carbon nucleophiles by enolization.[1] Recently, these strategies have been complemented by transition-metal-catalyzed functionalizations of the carbonyl C−H bond. In general, these reactions are based on the oxidative addition of the catalyst metal into the carbonyl C−H bond with the formation of an acyl-metal hydride as a key intermediate, which further reacts with olefins to afford the corresponding aliphatic ketones (Scheme 1a). After early reports of catalytic hydroacylation of alkenes with aldehydes by Miller[2] and Bosnich,[3] the scope of this type of reaction tremendously expanded both intra- and intermolecularly, giving linear or branched hydroacylation ketone products with high regio- or stereoselectivity.[4] For instance, Ryu's group[4j] and Krische's group[4k] independently realized intermolecular hydroacylation with the aldehyde's acyl group selectively added to the C3 position of the 2-substituted 1,3-butadiene. Similarly, the C−C double bond of conjugated alkenones as well as the C−C triple bonds can also be hydroacylated with aldehydes in different ways.[5,6]

Scheme 1. Different Approaches for Addition of Aldehydes to C−C Unsaturated Bonds



Recently, as a novel complement, we reported that aldehydes could also undergo decarbonylative addition to unsaturated bonds via a metal-aryl-CO-hydride complex intermediate (Scheme 1b).[7] During this process, the aryl and hydride parts added to the unsaturated bonds to afford the corresponding products while the carbonyl group was released as carbon monoxide in the form of waste. We reasoned that the released carbon monoxide could be reused in situ as a C1-building block. In continuation of our previous research, *we herein report a formal arylformylation of E-β-bromostyrenes with readily available aldehydes via a reshuffle of the aldehyde functionality with a loss of hydrogen bromide*, to give *E*-2-arylcinnamaldehydes highly selectively (Scheme 1c).

To test our hypothesis, *E*-β-bromo-*p*-methoxystyrene (**1a**) was reacted with benzaldehyde (**2a**) in the presence of 10 mol % of $[RuCl_2Cp^*]_n$. To our delight, the corresponding *E*-2-(4-methoxyphenyl) cinnamaldehyde (**3aa**) was detected when catalytic quantities of Cu-salts were added as a cocatalyst (Table 1, entries 1−4). A trace amount of the corresponding product was detected with $[RuCl_2Cp^*]_n$ together with small amounts of products due to debromination and halogen exchange; the combination of $[RuCl_2Cp^*]_n$ with CuI (possibly activating the C−Br bond) showed the highest catalytic activity, generating *E*-2-(4-methoxyphenyl) cinnamaldehyde (**3aa**) in 46% yield (Table 1, entry 4). Then, the introduction of a KI additive slightly increased the yield possibly by converting some of the vinyl bromide to the more active iodide *in situ* (Table 1, entry 5). Encouraged by these initial results, we screened a variety of other ruthenium or rhodium catalysts together with different copper cocatalysts (Table 1, entries 6−11; Table S1, entries 1−28). Unfortunately, none of them exhibited a better effect than the combination of $[RuCl_2Cp^*]_n$ and CuI. Among those additives examined, KI was better than other iodide salts while $AgBF_4$ nearly disabled the reaction completely (Table 1, entry 12; Table S1, entries 29−32). In addition, an excess amount of aldehyde decreased the yield drastically (Table 1, entry 13). Subsequently, PPh_3 and other nitrogen-containing ligands such as proline, phenanthroline, tetramethylethylenediamine, and *N*-monosubstituted glycines were examined, with *N*,*N*-dimethylglycine providing the highest yield analogous to

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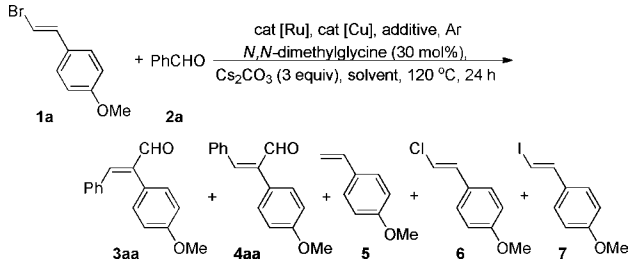
Table 1. Arylformylation under Various Conditions[a]



entry	mol % catalyst	additive (equiv)	solvent	% yield[b] 3aa/4aa/5/6/7
1	10% $[RuCl_2Cp^*]_n$	–	DMF	<10/–/16/14/–
2	10% $[RuCl_2Cp^*]_n$, 10% CuCl	–	DMF	<10/t[c]/ t/<10/–
3	10% $[RuCl_2Cp^*]_n$, 10% CuBr	–	DMF	25/–/ 21/t/–
4	10% $[RuCl_2Cp^*]_n$, 10% CuI	–	DMF	46/t/16/16/t
5	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	DMF	52/t/13/12/10
6	15% $Ru_3(CO)_{12}$, 10% CuI	KI (2)	DMF	t/–/ 29/–/27
7	10% $RuCp_2$, 10% CuI	KI (2)	DMF	45/–/14/–/25
8	10% $RuCl_2(PPh_3)_3$, 10% CuI	KI (2)	DMF	23/t/26/14/32
9	10% $RuCl_3{\cdot}3H_2O$, 10% CuI	KI (2)	DMF	14/t/14/27/18
10	10% $[RuCl_2Cp^*]_n$, 10% Cu dust	–	DMF	19/t/17/16/–
11	10% $[RuCl_2Cp^*]_n$, 10% Cu_2O	–	DMF	21/t/t/14/–
12	10% $[RuCl_2Cp^*]_n$, 10% CuI	LiI (2)	DMF	t/–/32/17/t
13[d]	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	DMF	22/t/26/14/11
14	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	dioxane	t/–/11/t/41
15	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	PhCl	t/–/t/t/t
16	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	xylene	32/–/10/t/10
17[e]	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	DMF	24/t/14/17/16
18[f]	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	DMF	47/t/25/10/10
19[g]	5% $[RuCl_2Cp^*]_n$, 5% CuI	KI (2)	DMF	66/t/14/t/13
20	5% $[RuCl_2Cp^*]_n$, 5% CuI	KI (0.2)	DMF	75/t/ <10/t/t
21[h]	10% $[RuCl_2Cp^*]_n$, 10% CuI	KI (2)	DMF	–/–/18/15/35

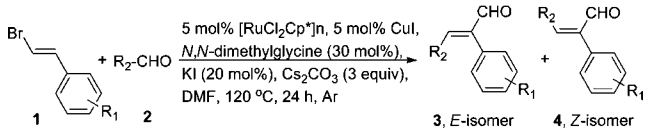
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), *N,N*-dimethylglycine (30 mol %), Cs_2CO_3 (3 equiv), solvent (0.3 mL), 120 °C, 24 h under argon, unless otherwise noted. The loading of the catalyst is based on the metal. [b]^{1}H NMR yields with nitromethane as the internal standard. [c]A trace amount. [d]0.5 mmol of **2a** was used. [e]At 100 °C. [f]At 140 °C. [g]20 mol % of *N,N*-dimethylglycine was used. [h]1 equiv of Cs_2CO_3 was used.

copper catalyzed Ullmann-type reactions of vinyl bromides with amines[8] (Table S2, entries 1–18).

Furthermore, a variety of bases and solvents were examined and the results showed that Cs_2CO_3 as the base and DMF as the solvent were most beneficial to this reaction (Table 1, entries 14–16; Table S2, entries 19–22). A higher or lower reaction temperature or a longer reaction time did not facilitate the reaction (Table 1, entries 17–18; Table S2, entry 23). However, modification of the loading of each item in the catalyst system influenced the reaction greatly: Reducing the amount of $[RuCl_2Cp^*]_n$ to 5 mol %, CuI to 5 mol %, and KI additive to 20 mol % afforded the highest yield (75%) of the desired product (Table 1, entry 20), whereas reducing the amount of ligand or the base resulted in a slightly lower yield or only a trace amount of the product, respectively (Table 1, entries 19, 21; Table S3).

With the optimized reaction conditions in hand, the substrate scope was explored at 120 °C under argon using 5 mol % of $[RuCl_2Cp^*]_n$ as the catalyst, 5 mol % of CuI as the cocatalyst, 30 mol % of *N,N*-dimethylglycine as the ligand, 20 mol % of KI as the additive, and 3 equiv of Cs_2CO_3 as the base in DMF for 24 h. As shown in Table 2, the reaction proceeded well with a wide range of substrates, giving *E*-2-arylcinnamaldehydes selectively. The ratio of *E*- to *Z*-isomer could reach up to 97:3 in several cases. Meanwhile, although the vinylic bromine was removed during the reaction, halogen on the aryl aldehyde could be tolerated, giving moderate to good yields of the corresponding product (Table 2, entries 5–8, 15–19). The electronic effect played an important role in this reaction. Generally, *E*-*β*-bromostyrenes with the methoxy group gave much better yields than those without any substituent, whereas the latter performed relatively better than those with the fluoro-substituent (Table 2, entries 1, 11, 19). In contrast, *E*-*β*-bromostyrenes without a substituent displayed slightly higher selectivity than those with the methoxy group to some extent. Yet, aliphatic aldehydes could not undergo this reshuffle,

Table 2. Scope of the Arylformylation[a]



entry	R^1	R^2	product	% yield[b] (*E*/*Z*)
1	**1a**, *p*-MeO	**2a**, Ph	**3aa+4aa**	72 (94:6)
2		**2b**, *p*-MeO-C_6H_4	**3ab+4ab**	65 (95:5)
3		**2c**, *p*-Me-C_6H_4	**3ac+4ac**	51 (94:6)
4		**2d**, *p*-Ph-C_6H_4	**3ad+4ad**	58 (93:7)
5		**2e**, *p*-CF_3-C_6H_4	**3ae+4ae**	77 (95:5)
6		**2f**, *p*-Cl-C_6H_4	**3af+4af**	68 (95:5)
7		**2g**, *m*-Cl-C_6H_4	**3ag+4ag**	79 (95:5)
8		**2h**, 3,4-Cl_2-C_6H_3	**3ah+4ah**	74 (95:5)
9		**2i**, 4-quinoline	**3ai+4ai**	34 (50:50)
10		**2j**, 3-pyridine	**3aj+4aj**	45 (83:17)
11	**1b**, H	**2a**, Ph	**3ba+4ba**	48 (96:4)
12		**2b**, *p*-MeO-C_6H_4	**3bb+4bb**	54 (95:5)
13		**2c**, *p*-Me-C_6H_4	**3bc+4bc**	39 (97:3)
14		**2d**, *p*-Ph-C_6H_4	**3bd+4bd**	25 (97:3)
15		**2e**, *p*-CF_3-C_6H_4	**3be+4be**	63 (97:3)
16		**2f**, *p*-Cl-C_6H_4	**3bf+4bf**	55 (97:3)
17		**2g**, *m*-Cl-C_6H_4	**3bg+4bg**	66 (95:5)
18		**2h**, 3,4-Cl_2-C_6H_3	**3bh+4bh**	60 (96:4)
19	**1c**, *m*-F	**2a**, Ph	**3ca+4ca**	44 (96:4)

[a]Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $[RuCl_2Cp^*]_n$ (5 mol %, based on Ru), CuI (5 mol %), *N,N*-dimethylglycine (30 mol %), KI (20 mol %), Cs_2CO_3 (3 equiv), DMF (0.3 mL), 120 °C, 24 h, under argon, unless otherwise noted. [b]Total isolated yields of *E*- and *Z*-isomers. The ratios of *E*- to *Z*-isomers are determined by ^{1}H NMR analysis.

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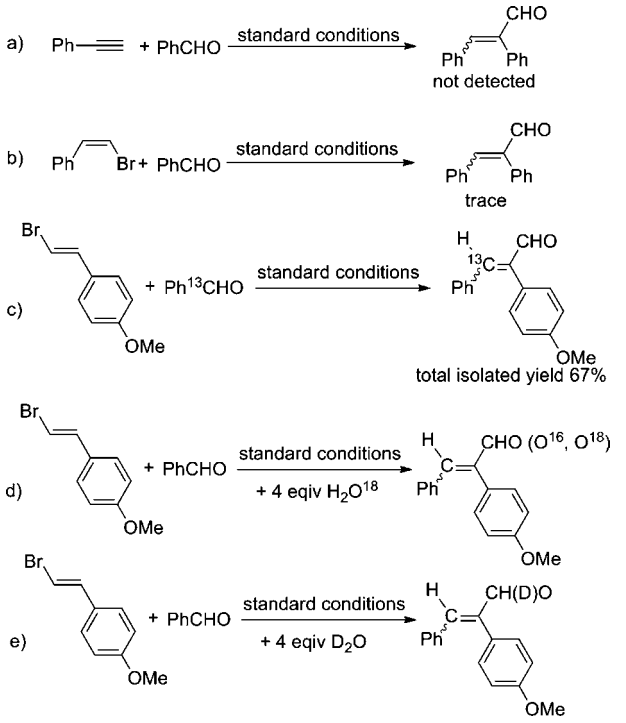
indicating chemoselectivity between aromatic and aliphatic aldehydes.

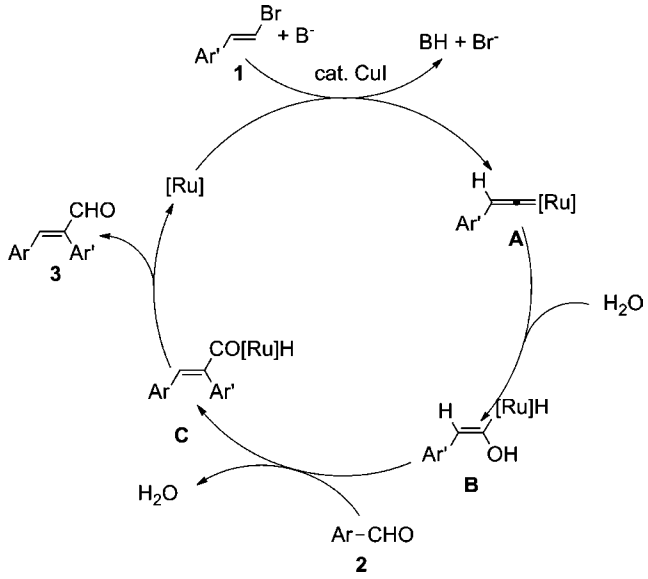
To explore the mechanism of the reaction, some control experiments were conducted under the optimized reaction conditions. The reaction of phenylacetylene with benzaldehyde gave neither *E*- nor *Z*-2-arylcinnamaldehyde product (Scheme 2a), suggesting that a potential *in situ* HBr elimination of *E*-*β*-bromostyrene was not involved in this reaction although the involvement of an alkynyl-metal intermediate could not be ruled out.[9] However, if *Z*-*β*-bromostyrene was introduced instead of the *E*- one, only trace amounts of *E*- and *Z*-products were detected, demonstrating the importance of the configuration of *β*-bromostyrenes (Scheme 2b). When ^{13}C-labeled benzaldehyde was used, to our great surprise, the ^{13}C was incorporated exclusively into the C=C bond (Scheme 2c). Yet, when ^{18}O-labeled water was added, both ^{16}O and ^{18}O products were obtained as a mixture (^{16}O:^{18}O = 2:1 ratio in GC/MS: *note, the actual ratio may not be correct*) (Scheme 2d). Similarly, the addition of D_2O also led to a mixture of both regular and deuterated products (Scheme 2e).

Scheme 2. Investigation of the Mechanism for the Arylformylation



With these experimental results, a tentative mechanism is postulated in Scheme 3: Initially, vinyl bromide **1** reacts with the active ruthenium catalyst together with a base to form the vinylidene intermediate **A**. CuI might have catalyzed this process (through the activation of the C−Br bond or through the Fenkelstein iodo-bromo exchange reaction to generate the more reactive vinyl iodide) and improved the yield. It should be noted that a direct conversion of vinyl iodide to a vinylideneplatinum species *via* a vinylplatinum intermediate was observed previously on the platinum surface during a gas-phase reaction in 1994.[10] However, we were unable to generate a vinylidene product under stoichiometric conditions. Subsequently, nucleophilic addition of water to **A** generates intermediate **B**,[11] which undergoes an aldol-type reaction with aldehyde **2** immediately to give intermediate **C** and regenerate water.[12] Finally, reductive elimination of **C** gives the final product **3** and regenerates the active ruthenium catalyst. It is also possible that the reductive elimination occurred first or a ruthenium-catalyzed direct conversion of the vinyl halide to generate a phenylacetaldehyde, which undergoes the aldol reaction to give the final product. However, phenylacetaldehyde was not detected in a control experiment with only the vinyl halide under the same reaction conditions. Furthermore, replacing vinyl bromide **1** with phenylacetaldehyde did not give any desired product under the same reaction conditions; thus a mechanism involving an initial hydrolysis of styrene bromide followed by an aldol reaction is unlikely. Another alternative mechanism involves a Ru(III)/CuI-catalyzed [2 + 2] cycloaddition of the two components to give 2-bromo-3,4-diaryloxetanes, which may undergo ring opening to give products directly. However, this is not consistent with the ^{16}O and ^{18}O isotope experiments. The exact mechanism of this transformation is still not clear at this stage and is under further investigation.

Scheme 3. Tentative Mechanism for the Arylformylation



In summary, we have developed an unprecedented reshuffle of the aldehyde functionality between the reaction of vinyl bromide and aryl aldehydes. The reaction provides a selective synthesis of *E*-2-arylcinnamaldehydes through a formal arylformylation of *E*-*β*-bromostyrenes with aldehydes. A broad range of substrates were examined, and an electronic effect was observed in this reaction. Further efforts to increase the reaction yield, to clarify the mechanism, and to expand the application of such a reaction to aliphatic aldehydes are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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