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Rh(I)-Catalyzed Decarboxylative Transformations of Arenecarboxylic Acids: Ligand- and Reagent-Controlled Selectivity toward Hydrodecarboxylation or Heck−Mizoroki Products

Zhong-Ming Sun, Jing Zhang, and Pinjing Zhao*

Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, North Dakota 58105-6050

pinjing.zhao@ndsu.edu

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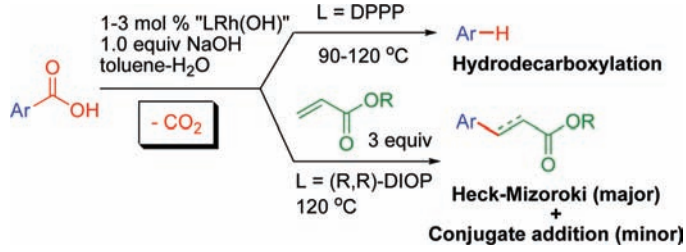
ABSTRACT



A Rh(I)-based catalyst system has been developed to promote three types of decarboxylative transformations of arenecarboxylic acids: (1) hydrodecarboxylation, (2) Heck−Mizoroki olefination, and (3) conjugate addition. Scopes of reactions (1) and (2) were studied, and the ligand and reagent dependence of selectivity was explored.

Late transition-metal-catalyzed decarboxylative transformations of arenecarboxylic acids have generated much interest in the past few years.[1] Advancements in this area would allow arenecarboxylic acids to be used as readily available and easy-to-handle building blocks in homogeneous catalysis. In a typical decarboxylation process, a transition metal aryl intermediate is generated by the release of CO_2.[2] Pioneering work by the Myers group has resulted in the discovery of Pd-catalyzed decarboxylative Heck−Mizoroki reactions,[3] which has inspired the expansion of this decarboxylation strategy for various catalytic reactions.[4−6] For example, Goo*β*en and co-workers have developed Pd- and Cu-catalyzed decarboxylative cross-couplings for biaryl synthesis.[4] Related decarboxylative cross-couplings have been reported by several other groups.[5] Other important examples include Pd-, Cu-, and Ag-catalyzed hydrodecarboxylations[6] and Rh- and Ir-catalyzed decarboxylative alkyne arylations.[7] From the mechanistic viewpoint, these decarboxylative

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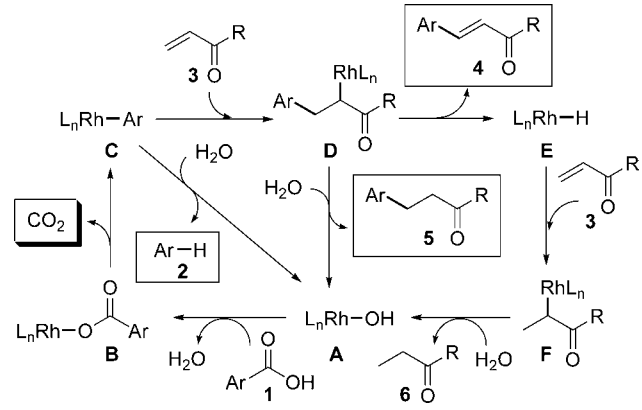
transformations of arenecarboxylic acids are also related to the recent studies on Cu- and Fe-catalyzed decarboxylative cross-couplings of α-amino acids reported by Li and co-workers.[8]

Despite the abundance in recent literature on catalytic decarboxylative reactions, there remains plenty of room for improvement. Some of the common challenges for existing methods include limited substrate scopes, relatively harsh reaction conditions (e.g., reaction temperatures of 150 °C and above), high catalyst loadings, and the requirement of a stoichiometric amount of heavy metal additives. In addition, most decarboxylation reactions were carried out in strongly polar solvents (e.g., DMF and DMSO), and studies of ligand effects on overall reactivity and selectivity are rare.[1,3f,4e] We herein report a study on decarboxylative formation of rhodium(I) aryl intermediates and its catalytic applications in the *selective* formation of hydrodecarboxylation and Heck−Mizoroki products.

Our previous results on Rh(I)-mediated stoichiometric decarboxylations[9] have led us to propose an overall mechanistic picture involving three potential catalytic cycles sharing common intermediates (Scheme 1): (1) Starting with a Rh(I) hydroxo complex **A**, reaction with acid **1** forms a Rh(I) carboxylato intermediate **B**. Subsequent release of CO_2 from **B** generates the key reactive intermediate of Rh(I) aryl complex **C**. In an aqueous reaction media, hydrolysis of **C** releases the arene product **2** and regenerates **A**, completing the first catalytic cycle (*hydrodecarboxylation*).[6] (2) Alternatively, intermediate **C** could undergo migratory insertion with added olefin substrates, such as a α,β-unsaturated carbonyl derivative **3**, forming a new C−C bond in a Rh(I) enolato intermediate **D**. Hydrolysis of **D** releases the conjugate addition product **5** and regenerates **A**, completing the second catalytic cycle (*decarboxylative conjugate addition*).[9−11] (3) β-Hydrogen elimination with intermediate **D** would release a Heck−Mizoroki product **4** and form a Rh(I) hydride **E**.[3,12] Among possible reactions of **E**, migratory insertion with the excess olefin **3** forms another Rh(I) enolate **F**. Subsequent hydrolysis of **F** releases a hydrogenation byproduct **6** and regenerates **A**, completing the third catalytic cycle (*decarboxylative Heck−Mizoroki olefination*).

Scheme 1. Working Hypothesis for Rh(I)-Catalyzed Decarboxylative Transformations of Arenecarboxylic Acids That Lead to Various Products



With our previous studies on Rh(I)-catalyzed decarboxylative conjugate additions in a mixed toluene−H_2O media,[9] we seek to modify our catalyst system for the selective formation of other desired products. Our efforts in catalyst development have been guided by the following mechanistic insights (Scheme 1): (1) the hydrodecarboxylation catalytic cycle would become the dominant pathway in an aqueous media and without added olefins, and the overall reactivity likely depends on a rate-limiting decarboxylation step (**B**→**C**). (2) Selectivity of Heck−Mizoroki vs conjugate addition products (**4**:**5**) is determined by competitive β-H elimination vs hydrolysis of the enolato intermediate **D**.[11] Both steps are expected to be significantly influenced by ligand effects,[12] and lower water content should slow down hydrolysis and favor Heck−Mizoroki product formation. (3) The use of excess olefin substrate **3** as a sacrificial hydrogen acceptor (**E**→**F**) provides an operationally simple alternative for the reported Pd-catalyzed decarboxylative Heck−Mizoroki reactions using Ag_2CO_3[3a−c] or 1,4-benzoquinone[3e] as oxidants.

We began our investigation by studying Rh(I)-catalyzed hydrodecarboxylation of arenecarboxylic acids, and selected results are summarized in Table 1. 2,6-Difluoro-4-methoxybenzoic acid (**1a**) was picked as a model substrate due to the high reactivity of *ortho*-fluorinated benzoic acids in our previous study on Rh(I)-catalyzed decarboxylative conjugate additions.[9] In addition, the relatively less volatile 1,3-difluoro-5-methoxybenzene (**2a**) allows convenient product characterization by GC analysis. Under the optimized conditions of $[(cod)Rh(OH)]_2$ (0.5 mol %), DPPP ligand (1.1 mol

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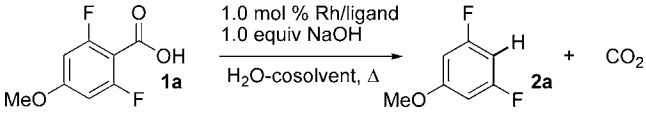
%), NaOH additive (1.0 equiv),[13] mixed solvent of toluene−H_2O (~7:1), and 110 °C, **1a** underwent smooth hydrodecarboxylation to give a near-quantitative yield within 12 h (entry 7). It is noteworthy that in contrast to the typical reaction media in Ag- or Pd-catalyzed protodecarboxylations[6] more polar solvents such as THF, dioxane, and DMF were detrimental to the current catalyst system (entries 15−17).

Table 1. Optimization of Rh-Catalyzed Protodecarboxylation[a]



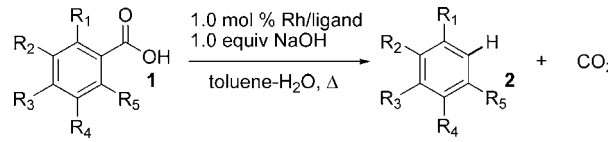
entry	ligand[b]	temp (°C)	cosolvent	**2a** yield (%)[c]
1	none	110	toulene	0
2	PEt_3	110	toulene	0
3	P^tBu_3	110	toulene	0
4	PPh_3	110	toulene	0
5	DPPMethane	110	toulene	<3
6	DIPHOS	110	toulene	78
7	DPPP	110	toulene	99
8	DPPB	110	toulene	95
9	DPPPentane	110	toulene	0
10	(rac)BINAP	110	toulene	54
11	BIPHEP	110	toulene	57
12	DPPF	110	toulene	31
13	DPPP	100	toulene	41
14[d]	DPPP	80	toulene	13
15[e]	DPPP	110	THF	68
16[e]	DPPP	110	dioxane	21
17[e]	DPPP	110	DMF	<5

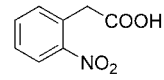
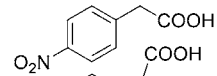
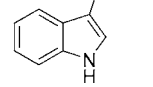
[a] Reaction conditions: **1a** (0.225 mmol, 1.0 equiv), NaOH (1.0 equiv), [(cod)Rh(μ-OH)]$_2$ (0.005 equiv), ligand (0.031 equiv of monophosphine, 0.011 equiv of bisphosphine), toluene−H_2O (1.0 mL/150 μL), 12 h. [b] Ligands: DPPMethane = bis(diphenylphosphino)-methane, DIPHOS = 1,2-bis(diphenylphosphino)ethane, DPPP = 1,3-bis(diphenylphosphino)-propane, DPPB = 1,4-bis(diphenylphosphino)butane, DPPPentane = 1,5-bis(diphenylphosphino)pentane, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl, DPPF = 1,1′-bis(diphenylphosphino)ferrocene. [c] GC yields. [d] 0.015/0.033 equiv of [(cod)Rh(μ−OH)]$_2$/ DPPP. [e] Cosolvent/H_2O (1.5 mL/0.2 mL), 24 h.

The hydrodecarboxylation reactivity was significantly influenced by phosphine ligands: no reaction occurred without any ligand or with monophosphine ligands (Table 1, entries 1−4). In comparison, reactivity increased using bisphosphine ligands with the ligand backbone increasing from 1- to 3-carbon, peaking with the DPPP ligand (entries 5−7). Lower reactivity was observed with bisphosphines of 4-carbon backbones (entries 8 and 10−11), while no reaction occurred with DPPPentane, which has a 5-carbon backbone (entry 9).

With the standard reaction conditions established, the substrate scope was explored for Rh(I)-catalyzed hydrodecarboxylation (Table 2). Consistent with our previous results on decarboxylative conjugate additions,[9] 2,6-difluorinated benzoic acids displayed excellent reactivities, forming the corresponding perfluorobenzenes in high yields within 12 h (entries 1−6). Replacing one of the *ortho*-fluorines with a methoxy or CF_3 group also led to high reactiviy (entries 7−9). In particular, satisfactory yield was achieved with 2,3,4,5-tetrafluoro-6-methoxybenzoic acid at a lower reaction temperature of 90 °C (entry 9). Further replacing both *ortho*-fluorines with methoxy or ethoxy groups reduced the reactivity to some extent, although high yields were still achievable with higher catalyst loadings (3% Rh) and elongated reaction time at 120 °C (entries 10−12).[14] Both *ortho*-substituents appeared to be important to promote decarboxylation reactivity.[9] For example, 2-fluorobenzoic acid reacted reluctantly at 150 °C, giving fluorobenzene in less than 10% yield (entry 13). Benzoic acid and 2-methoxybenzoic acid remained entirely unreactive under current catalytic conditions. The high catalyst efficiency prompted us to test other types of carboxylic acids that have been studied in catalytic decarboxylative transformations, and the preliminary results were quite encouraging: 2- and 4-nitrophenylacetic acids[15] and indole-3-carboxylic acid[3d] under-

Table 2. Substrate Scope of Rh-Catalyzed Protodecarboxylation[a]



entry	**1/2**	R_1	R_2	R_3	R_4	R_5	temp (°C)	time (h)	yield (%)[b]
1	**a**	F	H	OMe	H	F	110	12	(87)
2	**b**	F	Cl	H	H	F	110	12	(89)
3	**c**	F	F	H	H	F	110	12	(98)
4	**d**	F	H	F	H	F	110	12	(83)
5	**e**	F	F	F	F	F	110	8	(85)
6	**f**	F	H	H	H	F	110	10	(93)
7	**g**	F	H	H	H	OMe	110	12	(87)
8	**h**	F	H	H	H	CF_3	110	5	(83)
9	**i**	F	F	F	F	OMe	90	12	(92)
10[c]	**j**	OMe	H	H	H	OMe	120	30	71 (75)
11[d]	**k**	OMe	H	OMe	H	OMe	120	18	85 (92)
12[d]	**l**	OEt	H	H	H	OEt	120	24	92 (99)
13[d]	**m**	F	H	H	H	H	150	24	(8)
14[e]	**n**						**1n**	90	24	81 (92)
15[e]	**o**						**1o**	100	16	87 (96)
16	**p**						**1p**	100	24	85 (93)

[a] Reaction conditions: acid **1** (0.225 mmol, 1.0 equiv); NaOH (1.0 equiv); [(cod)Rh(μ-OH)]$_2$/DPPP (0.005/0.011 equiv); toluene−H_2O (0.8/0.15 mL). [b] Isolated yields; ^{19}F-NMR (entries 1−9) or GC yields (entries 10−15) listed in parentheses. [c] Using 1.5 mol % Rh dimer and 3.3 mol % DPPP; Na_2CO_3 in place of NaOH; toluene−H_2O (2.0 mL/200 μL). [d] Using 1.5 mol % Rh dimer and 3.3 mol % DPPP; toluene−H_2O (2.0 mL/200 μL). [e] Using 0.5 mol % Rh dimer and 1.1 mol % DPPP; THF−H_2O (2.0 mL/350 μL).

(13) See ref 9 for a discussion on the potential roles of added NaOH.

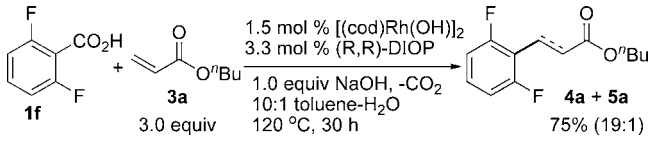
(14) A monodeuterated product **2l-d_1** was generated under analogous conditions using D_2O in place of H_2O, with near-quantitative deuterium incorporation at the expected 2-position (see Supporting Information).

(15) Pd-catalyzed decarboxylative allylation of nitrobenzene acetic esters: Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860.

went hydrodecarboxylation with a slightly modified protocol in THF−H_2O (entries 14−15), giving high product yields under mild reaction conditions (90−100 °C).

We then turned our attention to catalytic decarboxylative Heck−Mizoroki reactions. A model reaction between 2,6-difluorobenzoic acid (**1f**) and *n*-butyl acrylate (**3a**) has been previously investigated and reported.[9] While the general catalyst system was similar to that of hydrodecarboxylation, both the overall yield and the selectivity were highly dependent on the choice of phosphine ligand.[16] In Scheme 2, we summarized the optimized conditions that favored the Heck−Mizoroki product **4a** over the conjugate addition product **5a**. A combined yield of 75% and 19:1 selectivity of **4a**:**5a** was achieved using 1.5 mol % of $[(cod)Rh(OH)]_2$ and 3.3 mol % of the bisphosphine ligand (*R*,*R*)-DIOP.[17] A lower yield of 64% was observed when 2.0 equiv of **3a** was used instead of 3.0 equiv, although the 19:1 selectivity remained unchanged. The role of excess olefin as a sacrificial hydrogen acceptor was supported by the detection of butyl propionate as a byproduct (Scheme 1, formation of **6**).[11]

Scheme 2. Optimized Reaction Conditions for a Rh(I)-Catalyzed Decarboxylative Heck−Mizoroki Reaction



Under the established standard reaction conditions, **3a** was tested with other arenecarboxylic acids for Rh(I)-catalyzed decarboxylative Heck−Mizoroki olefination (Figure 1, products **4a**−**g**). With the exception of pentafluorobenzoic acid (product **4g**), 2,6-difluorinated benzoic acids all gave the desired olefin products in good yields and with high selectivities over conjugate addition. 2,4,6-Trimethoxybenzoic acid was less reactive toward **3a**, giving Heck−Mizoroki product **4l** in 54% yield together with 41% yield of the protodecarboxylation byproduct **2k**. For the scope of electron-poor olefin substrates, ethyl- and *tert*-butyl acrylate reacted with **1a** to give Heck−Mizoroki products **4h** and **4i** in good yields. *N*,*N*-Dimethylacrylamide and methyl vinyl ketone showed poor reactivity (Figure 1, product **4j**, **4k**), while less reactive substrates, such as 2-cyclohexen-1-one, ethyl (*E*)-2-crotonate, and styrene, were entirely unreactive.

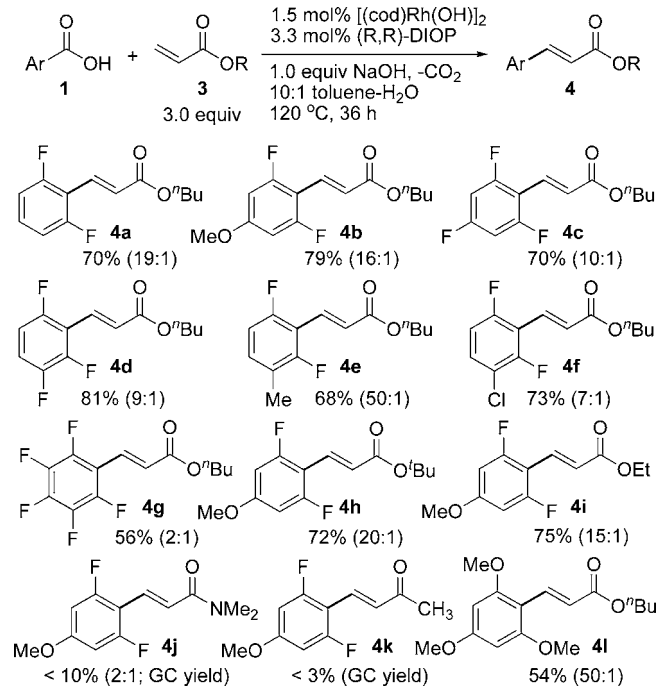


Figure 1. Isolated yields and selectivity of decarboxylative Heck−Mizoroki vs conjugate addition products under standard conditions.

In summary, a Rh(I)-based catalyst system has been developed for various decarboxylative transformations of *ortho*-substituted arenecarboxylic acids. By exploiting significant ligand and reagent effects on reaction pathways, highly selective formation of hydrodecarboxylation and Heck−Mizoroki products has been achieved with low catalyst loadings and under mild conditions. Current efforts are focused on further mechanistic probing to improve the catalyst efficiency and to overcome the limitation on substrate scopes.

Acknowledgment. Financial support for this work was provided by ND EPSCoR seed grant (EPS-0447679) and NDSU start-up fund. We thank Zhuo (Troy) Chen and Anthony F. X. Pillai of North Dakota State University for experimental assistance and Dr. Yong-Hua Yang of North Dakota State University for insightful discussions.

Supporting Information Available: Full experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For example, the DIPHOS, DPPP, and DPPB ligands, while being the best ligands to promote hydrodecarboxylation (Table 1), gave good to excellent overall yields yet very poor selectivities. In contrast, BIPHEP and racemic BINAP ligands efficiently promoted the formation of conjugate addition byproduct. Please see ref 9 for details.

(17) (*R*,*R*)-DIOP = (4*R*,5*R*)-(−)-4,5-bis(diphenylphosphanylmethyl)-2,2-dimethyl-1,3-dioxolane.