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Pd-Catalyzed Regiodivergent Hydroesterification of Aryl Olefins with Phenyl Formate

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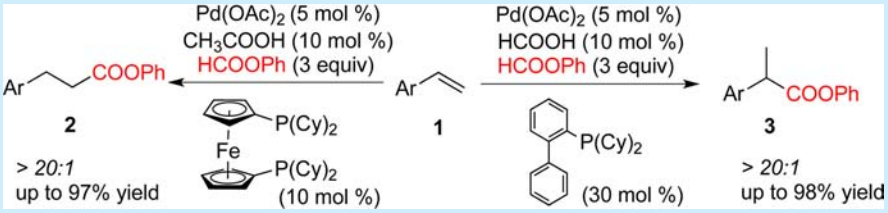
Supporting Information



ABSTRACT: An effective Pd-catalyzed regiodivergent hydroesterification of aryl olefins with phenyl formate is described. Either linear or branched phenyl arylpropanoates can be obtained in good yields with high regioselectivities by the judicious choice of ligand without the use of toxic CO gas.

Carboxylic esters are an important class of compounds in organic chemistry and play an important role in pharmaceuticals and fine chemicals. Hydroesterfication of olefins presents an attractive approach to this class of compound. Transition-metal catalyzed hydroesterification with CO has been intensively studied and provides a useful method for the synthesis of esters.[1,2] Nevertheless, CO is highly toxic and difficult to handle. Moreover, traditional processes are frequently carried out under high pressure and temperature. These drawbacks hamper the study and application of the hydroesterification in the laboratory. In the past, efforts have been made to use formates as CO surrogates to overcome the aforementioned disadvantages.[3,4] Regioselective hydroesterification of aryl olefins provides a straightforward approach to linear or branched arylpropanoates, which are useful intermediates for medicinally important compounds, such as nonsteroidal anti-inflammatory agents (Figure 1).[5] A number of examples have been reported with formates in the presence of a Ru[4j,l,n] or Pd[4i,k] catalyst. Generally, a mixture of linear or branched arylpropanoates have been obtained. Hydroesterification of aryl olefins with high regioselectivity still remains very challenging.[3c] During our ongoing studies on Pd-catalyzed CO-free hydrocarbonylation of olefins,[6] we have found that

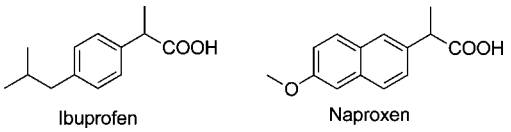
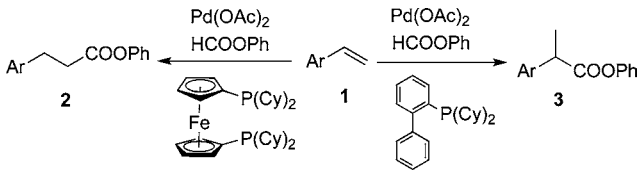


Figure 1. Examples of anti-inflammatory agents.

Scheme 1. Regiodivergent Hydroesterification of Olefins



either linear or branched phenyl arylpropanoates can be regioselectively formed from aryl olefins by the choice of ligand (Scheme 1). Herein, we wish to report our preliminary results on this subject.

Styrene (**1a**) was used as the test substrate for the hydroesterification. Various phosphine ligands were initially examined with 5 mol % $Pd(OAc)_2$ and 3.0 equiv of HCOOPh[4i,j] in toluene at 90 °C for 24 h. It was found that the ligand has a profound effect on the reaction efficiency and regioselectivity. The common bidentate ligands, such as dppe, dppp, dppb, and dppf, generally favored linear ester **2a** with up to 4:1 l/b ratio (Table 1, entries 1−4). When the phenyl group in dppf was replaced by a cyclohexyl group (**L1**[7]), compound **2a** was much more favored (with an 18:1 l/b ratio) (Table 1, entry 5). No regioselectivity was observed with Xantphos (**L2**) (Table 1, entry 6). No product was obtained with a cyclohexyl analogue of Xantphos (**L3**) (Table 1, entry 7). In contrast, the regioselectivity was reversed with PPh_3, favoring compound **3a** with a 1:3 l/b ratio (Table 1, entry 8). A slightly lower

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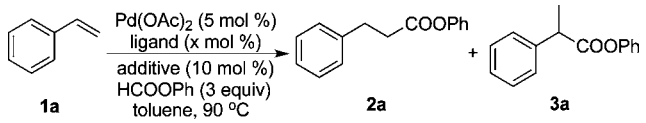
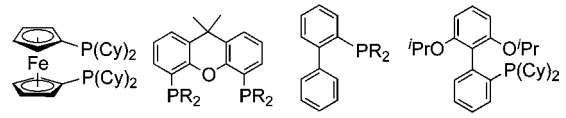
Table 1. Studies of the Reaction Conditions[a]

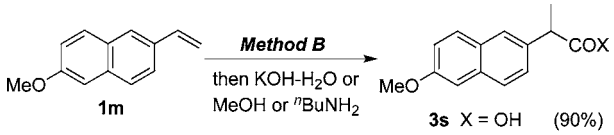


entry	ligand	additive	yield (%) (2a:3a)[b]
1	dppe		64 (2:1)
2	dppp		95 (4:1)
3	dppb		88 (4:1)
4	dppf		92 (2:1)
5	**L1**		88 (18:1)
6	**L2**		93 (1:1)
7	**L3**		0
8	PPh_3		89 (1:3)
9	**L4**		89 (1:2)
10	**L5**		45 (<1:20)
11	P(*o*-tolyl)$_3$		0
12	**L6**		trace
13	**L1**	$MeSO_3H$	28 (>20:1)
14	**L1**	HCOOH	89 (>20:1)
15	**L1**	CH_3COOH	92 (>20:1)
16[c]	**L1**	CH_3COOH	83 (>20:1)
17	**L5**	CH_3COOH	53 (<1:20)
18	**L5**	HCOOH	67 (<1:20)
19[d]	**L5**	HCOOH	92 (<1:20)
20[c,d]	**L5**	HCOOH	82 (<1:20)
21[e]	**L1**	HCOOH	0
22[e]	**L5**	HCOOH	0
23[f]	**L1**	HCOOH	0
24[f]	**L5**	HCOOH	0



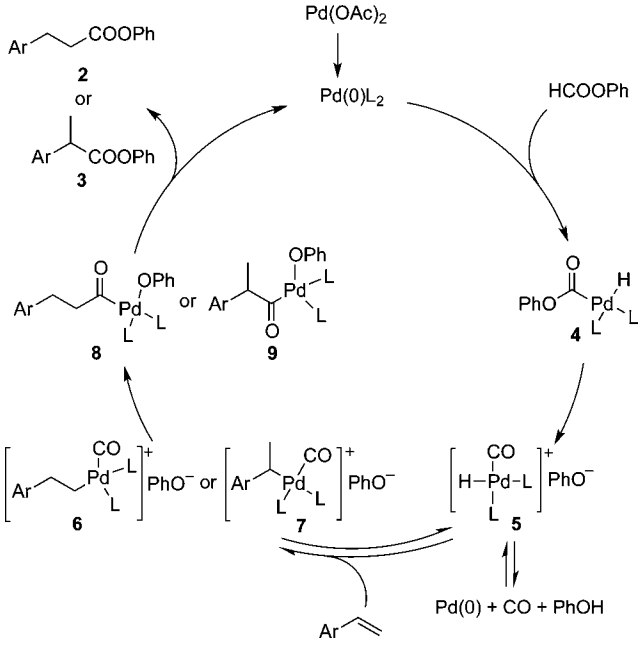
[a]The reactions were carried out with **1a** (0.50 mmol), HCOOPh (1.50 mmol), $Pd(OAc)_2$ (0.025 mmol), ligand (0.050 or 0.10 mmol, P/Pd = 4:1), and additive (0.050 mmol) in toluene (0.10 mL) at 90 °C for 24 h unless otherwise stated. [b]Isolated yield. The ratio of **2a**:**3a** was determined by ^{1}H NMR analysis of the crude reaction mixture. [c]HCOOPh at 1.00 mmol. [d]Ligand at 0.15 mmol. [e]The reaction was carried out with 3.0 equiv of HCOO^{n}Bu instead of HCOOPh. [f]The reaction was carried out with 3.0 equiv HCOOH in the absence of HCOOPh.

Scheme 2. Synthetic Transformations



selectivity was obtained with 2-(diphenylphosphino)biphenyl (**L4**) (Table 1, entry 9). Again, compound **3a** was greatly favored (with a <1:20 l/b ratio) with a cyclohexyl analogue of ligand **L4**, and a relatively lower yield was obtained (Table 1, entry 10). Little product was detected with P(*o*-tolyl)$_3$ and **L6** (Table 1, entries 11 and 12). Similar yield and regioselectivity were obtained for the reaction with **L1** by addition of 10 mol % HCOOH or CH_3COOH (Table 1, entries 14 and 15 vs entry 5). However, in the case of **L5**,[8] the yield increased from 45 to 67% with 10 mol % HCOOH (Table 1, entry 18 vs entry 10). The exact role of the acid is not currently clear; the acid could facilitate the reaction by activating HCOOPh. Studies showed that the yield was further increased to 92% with more ligand added (Table 1, entry 19). The yield was decreased when the amount of HCOOPh was reduced (Table 1, entries 16 and 20). Control experiments showed that no ester products were observed when HCOO^{n}Bu was used instead of HCOOPh (Table 1, entries 21 and 22). When the reaction was carried out with 3.0 equiv of HCOOH in the absence of HCOOPh, the reduction product (ethylbenzene) was mainly formed (Table 1, entries 21–24).

Scheme 3. Proposed Catalytic Cycle for Regioselective Hydroesterification



The regiodivergent hydroesterification can be extended to a wide variety of aryl olefins. Either linear or branched phenyl arylpropanoates can be obtained in 54–98% yields with high regioselectivities with ligand **L1** or **L5** (Table 2, entries 1–16). Substituted styrenes were effective substrates. The phenyl rings can have various substituents, including OMe, alkyl, phenyl, Cl, and CF_3 groups (Table 2, entries 1–11). The hydroesterification also worked well for olefins with other aromatics, such as naphthalene and thiophene (Table 2, entries 12–16). For alkyl terminal olefins, linear esters were formed predominately under both conditions (methods A and B) (Table 2, entries 17 and 18). Further studies showed that the regioselectivity for the linear ester with 1-hexene (**1q**) was increased to >20:1 when 1,1′-bis(di-*tert*-butylphosphino)-ferrocene was used as ligand (Table 2, entry 17, method C). For *β*-methylstyrene (*cis* and *trans* mixture), a mixture of phenyl 4-phenylbutanoate (**11**), phenyl 2-methyl-3-phenyl-propanoate (**12**), and phenyl 2-phenylbutanoate (**13**) was isolated in 50% yield with a ratio of 100:7:1 when the reaction was carried out with method A. When method B was used, a mixture of phenyl 4-phenylbutanoate (**11**) and phenyl 2-phenylbutanoate (**13**) (1:45) was obtained in 21% yield.

The branched esters from 1-isobutyl-4-vinylbenzene and 2-methoxy-6-vinylnaphthalene (Table 2, entries 3 and 13) are

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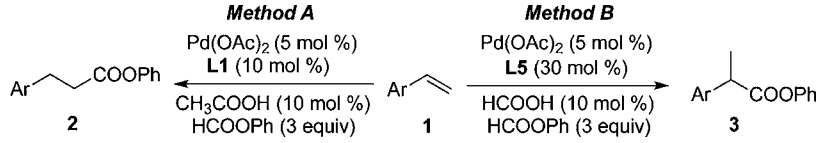
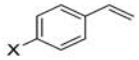
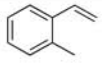
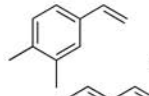
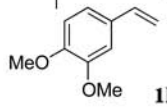
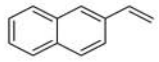
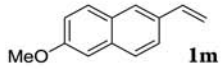
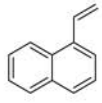
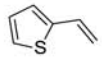
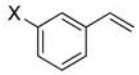
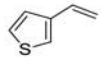
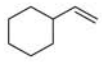
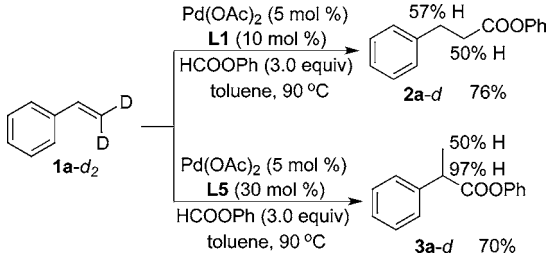
Table 2. Pd-Catalyzed Regiodivergent Hydroesterification of Olefins



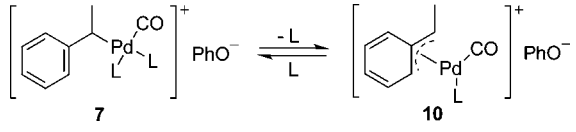
entry	1	method[a]	yield(%) (2:3)[b]	entry	1	method[a]	yield(%) (2:3)[b]
				9	 **1i**	A	91 (> 20:1)
						B	97 (< 1:20)
1	X = H **1a**	A	92 (> 20:1)	10	 **1j**	A	97 (> 20:1)
		B	92 (< 1:20)			B	98 (< 1:20)
2	X = OMe **1b**	A	85 (> 20:1)	11	 **1k**	A	93 (12:1)
		B	90 (< 1:20)			B	96 (< 1:20)
3	X = ^{t}Bu **1c**	A	88 (> 20:1)	12	 **1l**	A	85 (> 20:1)
		B	98 (< 1:20)			B	96 (< 1:20)
4	X = Ph **1d**	A	85 (> 20:1)	13	 **1m**	A	84 (> 20:1)
		B	93 (< 1:20)			B	98 (< 1:20)
5	X = Cl **1e**	A	83 (> 20:1)	14	 **1n**	A	62 (> 20:1)
		B	91 (< 1:20)			B	54 (< 1:20)
6	X = CF_3 **1f**	A	77 (18:1)	15	 **1o**	A	65 (> 20:1)
		B	62 (< 1:20)			B	77 (< 1:20)
				16	 **1p**	A	81 (> 20:1)
						B	87 (< 1:20)
7	X = Me **1g**	A	95 (> 20:1)	17[c]	 **1q**	A	86 (9:1)
		B	96 (< 1:20)			B	25 (4:1)
						C	51 (> 20:1)
8	X = OMe **1h**	A	94 (> 20:1)	18[c]	 **1r**	A	57 (> 20:1)
		B	93 (< 1:20)			B	42 (> 20:1)

[a]Method A: The reactions were carried out with **1** (0.50 mmol), HCOOPh (1.50 mmol), $Pd(OAc)_2$ (0.025 mmol), **L1** (0.050 mmol), and CH_3COOH (0.050 mmol) in toluene (0.10 mL) at 90 °C for 24 h unless otherwise stated. Method B: The reactions were carried out with **1** (0.50 mmol), HCOOPh (1.50 mmol), $Pd(OAc)_2$ (0.025 mmol), **L5** (0.150 mmol), and HCOOH (0.050 mmol) in toluene (0.10 mL) at 90 °C for 24 h unless otherwise stated. Method C: The reaction was carried out with **1q** (0.50 mmol), HCOOPh (1.50 mmol), $Pd(OAc)_2$ (0.025 mmol), 1,1′-bis(di-*tert*-butylphosphino)ferrocene (0.050 mmol), and HCOOH (0.050 mmol) in toluene (0.10 mL) at 90 °C for 24 h. [b]Isolated yield and the ratio of two regioisomers was determined by ^1H NMR analysis of the crude reaction mixture. [c]The reaction mixture was stirred at 90 °C for 48 h.

Scheme 4. Deuterium-Labeling Experiments



Scheme 5. Palladium η^1–η^3 Benzyl Complexes



closely related to ibuprofen and naproxen (Figure 1). Phenyl esters are reactive intermediates. The corresponding acid, methyl ester, and amide can be readily obtained by direct addition of KOH-H_2O, MeOH, and *n*-butylamine to the reaction mixture at the end of hydroesterification (Scheme 2).

A precise reaction mechanism is not clear at this moment and requires further study. One plausible catalytic cycle is proposed in Scheme 3. The oxidative addition of Pd(0) to HCOOPh led to palladium hydride complex **4**, which rearranged to palladium carbonyl complex **5**. The olefin substrate was subsequently hydropalladated to form complexes **6** and **7**, which gave acylpalladium complexes **8** and **9** upon a migratory insertion. The reduction elimination of complexes **8** and **9** led to esters **2** and **3** with regeneration of the Pd catalyst.

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To further probe the reaction mechanism, we subjected deuterium-labeled styrene **1a**-d_2 to the hydroesterification reaction conditions (Scheme 4). With bidentate ligand **L1**, the resulting linear ester has 50% H at the α-carbon to the ester group. With monodentate ligand **L5**, the corresponding branched ester has 50% H at the β-carbon to the ester group. These results indicate that there is some deuterium−hydrogen exchange in both cases, suggesting that the hydropalladation process from **5** to complexes **6** and **7** is reversible and unlikely to be the determining step for the regioselectivity. The regioselectivity is likely to be determined in the subsequent migratory insertion step (from **6** and **7** to **8** and **9**). Palladium η^1-benzyl complex **7** can undergo ligand dissociation with monodentate ligand **L5** to form stabilized η^3-benzyl complex **10**,[9] which likely facilitates the formation of acylpalladium species **9**, leading to branched ester **3**. The formation of η^3-benzyl complex **10** is less favored for bidentate ligand **L1** due to the ligand dissociation being less facile than that of monodentate ligand **L5**. As a result, acylpalladium species **8** is favored due to the steric effect, leading to linear ester **2**. In the case of nonaromatic olefins (Table 2, entries 17 and 18), there exists no benzylic stabilization for the palladium species. Linear ester **2** is thus formed as the major product with both ligands **L1** and **L5** as a result of steric effects.

In summary, we have developed an efficient Pd-catalyzed regiodivergent hydroesterification of aryl olefins with phenyl formate under mild reaction conditions by a judicious choice of ligand. A wide variety of linear or branched phenyl arylpropanoates have been obtained with high yields and excellent regoselectivities. The reaction process is potentially useful for organic synthesis and operationally simple, requiring no handling of toxic CO gas. Further efforts will be devoted to understanding the reaction mechanism, expanding the substrate scope, and developing an asymmetric process of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra, and CIF information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01630.

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Notes

The authors declare no competing financial interest.

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