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Palladium-Catalyzed Highly Regio- and Enantioselective Hydroesterification of Aryl Olefins with Phenyl Formate

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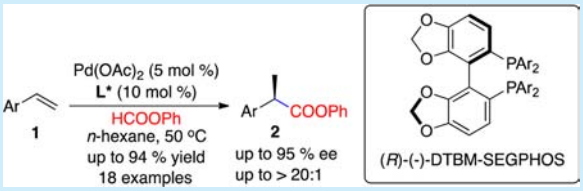
Supporting Information

ABSTRACT: An effective Pd-catalyzed regio- and enantioselective hydroesterification of aryl olefins with phenyl formate is described. A variety of phenyl 2-arylpropanoates can be obtained in good yields with high b/l ratios and ee's without using toxic CO gas.



Carboxylic esters are an important class of compounds for organic synthesis, pharmaceuticals, and fine chemicals. For example, 2-arylpropanoates can serve as useful intermediates for medicinally significant molecules such as nonsteroidal anti-inflammatory agents including ibuprofen, naproxen, ketoprofen, and fenoprofen (Figure 1).[1] Asymmetric hydroesterification of olefins would provide an attractive approach to optically active esters (Scheme 1). During the past 40 years, various asymmetric hydroesterification (as well as hydrocarboxylation) processes have been developed with a certain degree of success.[2−5] For example, very recently, Clarke and co-workers showed that asymmetric hydrocaboxylation of styrene was achieved with the Pd-phanephos catalyst in the presence of CO (30 bar) and H_2O, giving the corresponding acid in 91% ee with a 0.95 b/l ratio.[5f] In their subsequent studies, the corresponding methyl ester was obtained in 93% ee with 4:1 b/l ratio or 79% ee with >100:1 b/l ratio when the reaction was carried out with a related catalytic system in the presence of MeOH.[5g] In general, achieving high enantioselectivity for the hydroesterification or hydrocarboxylation process is challenging. Thus far, high ee's have been obtained with only limited number of styrenes.[4,5] Developing the reaction processes with both high regio- and enantioselectivity presents a formidable challenge and is highly desirable. In addition, the reactions have been traditionally carried out with toxic CO gas under high pressure and/or high temperature, which could hamper exploration of them and use in laboratories. Herein, we wish to report a Pd-catalyzed highly regioselective and enantioselective hydroesterification of various aryl olefins with phenyl formate,[6] requiring no handling of toxic CO gas (Scheme 2).[7]

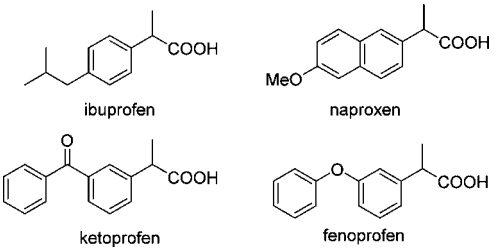
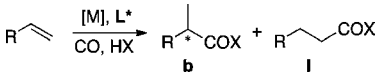
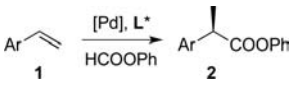


Figure 1. Examples of biologically important 2-arylpropanoic acids.

Scheme 1. Hydroesterification of Terminal Olefins



Scheme 2. Regio- and Enantioselective Hydroesterification



Styrene (**1a**) was used as the test substrate for the initial studies. The reactions were carried out with 5 mol % $Pd(OAc)_2$, a chiral ligand (Figure 2), and 3 equiv of HCOOPh in toluene at 90 °C (Table 1, entries 1−14). Trace ester products were detected with ligands **L1**−**L5** (Table 1, entries 1−5). With **L6** and **L7**, the esters were formed in 5−10% crude yields, favoring the linear ester (**3a**) (Table 1, entries 6 and 7). However, the catalyst activity greatly increased with **L8**−**L14**. Esters **2a** and **3a** were obtained in 82−99% crude yields with a 1:1 b/l ratio and 13−62% ee's (Table 1, entries 8−14). With (*R*)-(−)-DTBM-SEGPHOS[8] as the ligand, additional Pd catalysts were subsequently examined (Table 1, entries 15−18). A lower ee and more linear ester were obtained with $Pd(NO_3)_2$. With $Pd(TFA)_2$, the linear ester (**3a**) was formed almost exclusively. A small amount of esters was detected with $PdCl_2$ and $Pd(dba)_2$. The reaction temperature was found to be an important factor for both regio- and enantioselectivity (Table 1,

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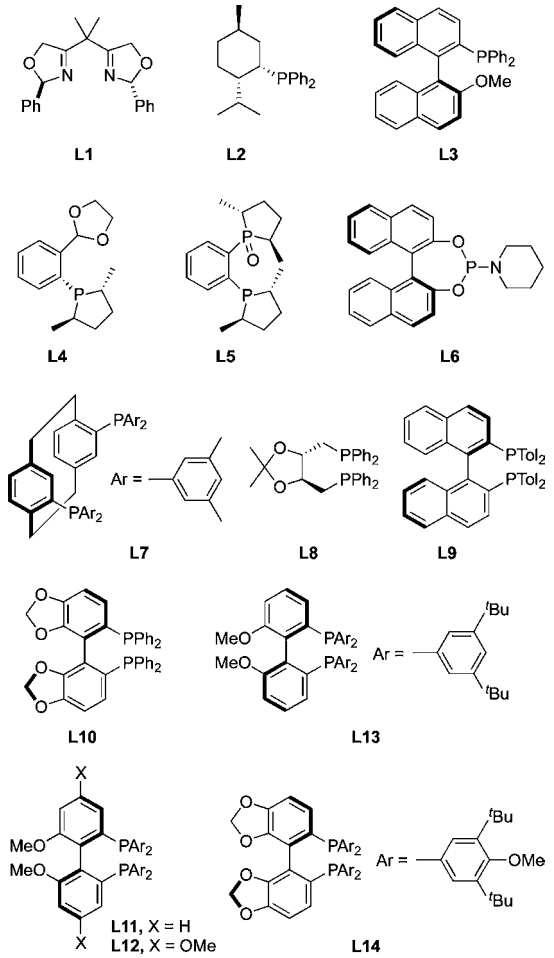
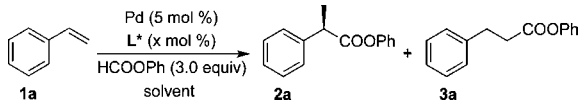


Figure 2. Examples of ligands examined.

entries 14, 19, and 20). When the reaction was carried out at 70 °C, esters **2a** and **3a** were formed in 94% crude yield with a 5:1 b/l ratio and 87% ee (Table 1, entry 19). The b/l ratio and ee were further improved when the reaction temperature was lowered to 50 °C while the yield was significantly reduced (Table 1, entry 20). However, no esters were detected at 40 °C (Table 1, entry 21). Further studies showed that the solvent had a large impact on the reaction outcome. Little reaction occurred with THF and EtOAc at 50 °C (Table 1, entries 22 and 23). With acetone, the branched ester (**2a**) was formed predominately, but the yield was low (Table 1, entry 24). High yield but low ee were obtained with CH_3CN (Table 1, entry 25). To our delight, ester **2a** was isolated in 92% yield with a 14:1 b/l ratio and 93% ee when the reaction was carried out in *n*-hexane (Table 1, entry 26).[9] Under these reaction conditions, other formats such as HCOOMe, HCOOBu, 2,6-dimethylphenyl formate, and 2,4,6-trichlorophenyl formate were found to be ineffective (Table 1, entries 27–30).

With the optimized reaction conditions in hand, the substrate scope for the asymmetric hydroesterification reaction was investigated. As shown in Table 2, the reaction can be extended to a wide variety of aryl olefins. *para*-Substituted styrenes were found to be effective substrates, giving the corresponding phenyl 2-arylpropanoates in 76–93% yield and 90–95% ee (Table 2, entries 1–8) (the X-ray structure of ester **2e** is shown in Figure 3). The reaction also proceeded highly regioselectively with the b/l ratio ranging from 11:1 to >20:1. The substituent can be both electron-donating and -withdrawing groups including OMe, alkyl, phenyl, Cl, F, and CF_3 groups. Similar results were obtained for

Table 1. Studies on the Reaction Conditions[a]



entry	Pd	ligand	temp (°C)	yield[b] (%) (**2a**:**3a**)[c]	ee (%)
1	$Pd(OAc)_2$	**L1**	90	NR	–
2	$Pd(OAc)_2$	**L2**	90	NR	–
3	$Pd(OAc)_2$	**L3**	90	NR	–
4	$Pd(OAc)_2$	**L4**	90	NR	–
5	$Pd(OAc)_2$	**L5**	90	NR	–
6	$Pd(OAc)_2$	**L6**	90	5 (0:1)	–
7	$Pd(OAc)_2$	**L7**	90	10 (1:4)	–
8	$Pd(OAc)_2$	**L8**	90	87 (1:1)	13
9	$Pd(OAc)_2$	**L9**	90	90 (1:1)	49
10	$Pd(OAc)_2$	**L10**	90	82 (1:1)	55
11	$Pd(OAc)_2$	**L11**	90	93 (1:1)	57
12	$Pd(OAc)_2$	**L12**	90	99 (1:1)	58
13	$Pd(OAc)_2$	**L13**	90	97 (1:1)	62
14	$Pd(OAc)_2$	**L14**	90	99 (1:1)	62
15	$Pd(NO_3)_2$	**L14**	90	88 (1:3)	49
16	$Pd(TFA)_2$	**L14**	90	62 (1:60)	–
17	$PdCl_2$	**L14**	90	NR	–
18	$Pd(dba)_2$	**L14**	90	NR	–
19	$Pd(OAc)_2$	**L14**	70	94 (5:1)	87
20	$Pd(OAc)_2$	**L14**	50	40 (12:1)	93
21	$Pd(OAc)_2$	**L14**	40	NR	–
22[d]	$Pd(OAc)_2$	**L14**	50	NR	–
23[e]	$Pd(OAc)_2$	**L14**	50	NR	–
24[f]	$Pd(OAc)_2$	**L14**	50	12 (1:0)	–
25[g]	$Pd(OAc)_2$	**L14**	50	99 (1:2)	27
26[h]	$Pd(OAc)_2$	**L14**	50	92[i] (14:1)	93
27[j]	$Pd(OAc)_2$	**L14**	50	NR	–
28[k]	$Pd(OAc)_2$	**L14**	50	NR	–
29[l]	$Pd(OAc)_2$	**L14**	50	NR	–
30[m]	$Pd(OAc)_2$	**L14**	50	13 (0:1)	–

[a]The reactions were carried out with **1a** (0.20 mmol), HCOOPh (0.60 mmol), $Pd(OAc)_2$ (0.010 mmol), ligand (0.020 or 0.040 mmol, P/Pd = 4:1), and toluene (0.20 mL) in a 4.0 mL vial for 24 h unless otherwise stated. [b]The yield was determined from a crude reaction mixture by ^{1}H NMR with 1-methoxy-4-methylbenzene as an internal standard. [c]The ratio of **2a**:**3a** was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]With THF (0.20 mL). [e]With EtOAc (0.20 mL). [f]With acetone (0.20 mL). [g]With CH_3CN (0.20 mL). [h]With *n*-hexane (0.20 mL). [i]Isolated yield. [j]With HCOOMe (0.60 mmol). [k]With HCOOBu (0.60 mmol). [l]2,6-Dimethylphenyl formate (0.60 mmol). [m]With 2,4,6-trichlorophenyl formate (0.60 mmol).

meta-substituted styrenes. The branched esters were isolated in 86–94% yield and 90–95% ee with a 14:1 to >20:1 b/l ratio (Table 2, entries 9–13). A slightly lower yield and regioselectivity were obtained for *ortho*-methylstyrene, possibly due to the steric effect (Table 2, entry 14). The hydroesterification was also effective for disubstituted styrenes, giving the corresponding ester products in 60–90% yield and 91–93% ee with a 10:1 to >20:1 b/l ratio (Table 2, entries 15–17). When 2-methoxy-6-vinylnaphthalene was subjected to the reaction conditions, the ester was isolated in 74% yield and 87% ee with an 8:1 b/l ratio (Table 2, entry 18). Heterocyclic olefins appeared to be ineffective substrates for the reaction. For example, small amounts of products were observed when 2-phenyl-5-vinylfuran and 4-vinylpyridine were subjected to the reaction conditions.

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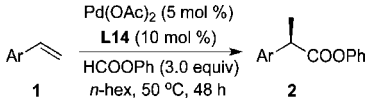
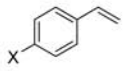
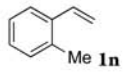
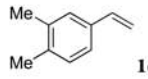
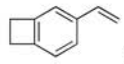
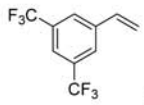
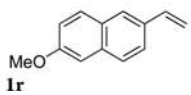
Table 2. Pd-Catalyzed Regio- and Enantioselective Hydroesterification of Olefins[a]



entry	substrate (1)	yield(%)[b] (b:l)[c]	ee(%)[d]
			
1	X = H, **1a**	84 (18:1)	95
2	X = OMe, **1b**	90 (11:1)	93
3	X = ^{t}Bu, **1c**	92 (16:1)	94
4	X = Me, **1d**	91 (15:1)	94
5	X = Ph, **1e**	93 (> 20:1)	95
6	X = Cl, **1f**	88 (> 20:1)	94
7	X = F, **1g**	76 (20:1)	95
8	X = CF_3, **1h**	84 (> 20:1)	90
			
9	X = OMe, **1i**	94 (> 20:1)	95
10	X = Me, **1j**	91 (14:1)	94
11	X = Cl, **1k**	92 (17:1)	93
12	X = F, **1l**	91 (17:1)	94
13	X = CN, **1m**	86 (> 20:1)	90
14	 **1n**	65 (4:1)	90
15	 **1o**	90 (10:1)	93
16	 **1p**	70 (11:1)	92
17	 **1q**	60 (> 20:1)	91
18	 **1r**	74 (8:1)	87

[a]The reactions were carried out with olefin (**1**) (0.50 mmol), HCOOPh (1.50 mmol), $Pd(OAc)_2$ (0.025 mmol), **L14** (0.050 mmol), and *n*-hexane (0.50 mL) in an 8.0 mL vial at 50 °C for 48 h. [b]Isolated yield. [c]The b/l ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]For entry 1, the absolute configuration was determined by comparing the optical rotation with the reported value.[10a] For entries 3, 6, 8, and 18, the absolute configurations were determined by comparing the optical rotations of the corresponding acids with the reported values.[10b] For entries 2, 4, 5, 7, and 9−17, the absolute configurations were tentatively assigned by analogy.

As illustrated in Scheme 3, the asymmetric hydroesterification reaction can be carried out on a gram scale with 1-isobutyl-4-vinylbenzene as the substrate. The (*S*)-enantiomer of the

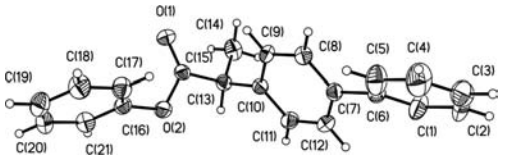
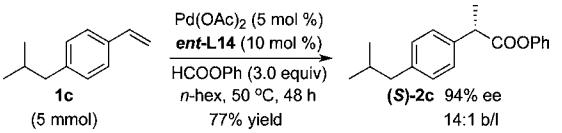


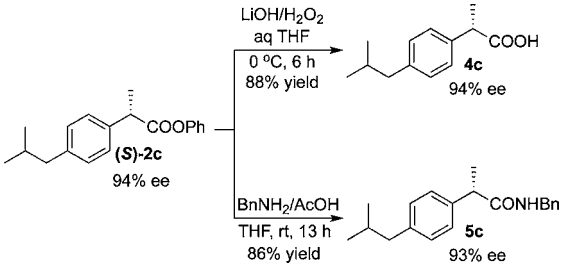
Figure 3. X-ray structure of ester **2e**.

Scheme 3. Gram-Scale Synthesis



corresponding ester was isolated in 77% yield and 94% ee with a 14:1 b/l ratio using *ent*-**L14** as the ligand. The resulting phenyl ester can be hydrolyzed with $LiOH/H_2O_2$[11] to give acid **4c** (ibuprofen) in 88% yield without loss of ee (Scheme 4). As an

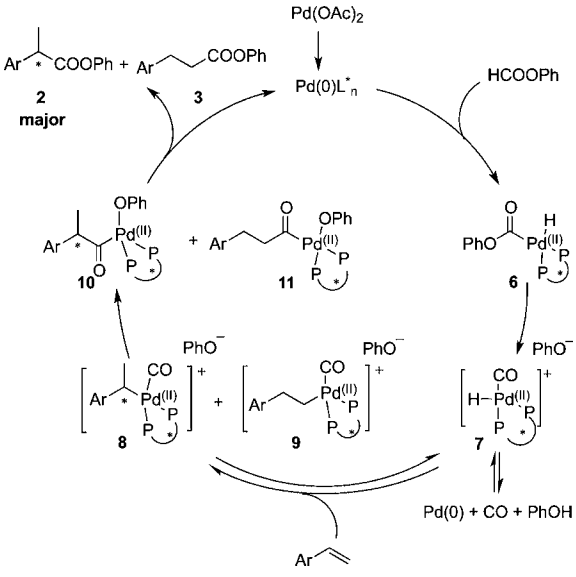
Scheme 4. Synthetic Transformations



active intermediate, the phenyl ester could be converted to other carboxyl acid derivatives. For example, when the ester was treated with $BnNH_2$/AcOH at rt for 13 h, the corresponding amide (**5c**) was isolated in 86% yield and 93% ee (Scheme 4).

A precise reaction mechanism requires further study. A plausible catalytic cycle is proposed in Scheme 5.[12] The Pd(0) is oxidatively inserted to HCOOPh to give palladium hydride

Scheme 5. Proposed Catalytic Cycle for Regio- and Enantioselective Hydroesterification



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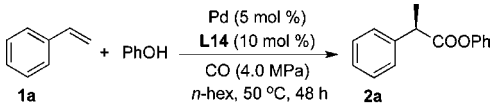
complex **6**, which was converted to palladium carbonyl complex **7** upon rearrangement. The hydropalladation of the olefin by **7** led to complexes **8** and **9**, which gave acylpalladium complexes **10** and **11** upon migratory insertion. Upon reductive elimination, **10** and **11** were converted to esters **2** and **3** with regeneration of the Pd catalyst. In the current reaction process, ester **2** was formed as a major product with **L14** as the ligand. The regioselectivity was likely due to the fact that complex **8** could be stabilized by the phenyl group and favored over **9**.[12]

The reactions were also carried out with CO gas and phenol instead of phenyl formate (Scheme 6). While similar enantioselectivities were observed as compared to phenyl formate, lower yields were obtained. The b/l ratio was found to be dependent upon the amount of phenol.

Scheme 6. Hydroesterification with CO Gas



PhOH: 1.2 equiv, 39% yield, 92% ee, >20:1 b/l
3.0 equiv, 41% yield, 93% ee, 3:1 b/l

In summary, we have developed an efficient Pd-catalyzed regio- and enantioselective hydroesterification of aryl olefins with phenyl formate using (*R*)-(−)-DTBM-SEGPHOS (**L14**) as the ligand under mild reaction conditions. A wide variety of phenyl 2-arylpropanoates can be obtained in high yield with excellent ee and b/l selectivity. To the best of our knowledge, the current system presents a rare example of an asymmetric hydroesterification process with cocurrentlly high regio- and enantioselectivity. In addition, the reaction process is operationally simple and requires no handling of toxic CO gas, which provides a potentially useful method for the synthesis of optically active 2-arylpropanoates and their derivatives. Further efforts will be devoted to understanding the reaction mechanism, developing more effective catalytic systems, and expanding the substrate scope.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02467.

Experimental procedures, characterization data, NMR spectra (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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(2) For leading reviews on hydroesterification with CO gas, see: (a) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435. (b) Ali, B. E.; Alper, H. In *Transition Metals for Organic Synthesis*, Vol. *1*, 2nd ed.; Beller, M., Bolm, C., Eds.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; pp 113−132. (c) Brennführer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28.

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