Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated *N*-Acylamides Catalyzed by Dicationic Palladium(II)–(*S*,*S*)-Chiraphos Complex

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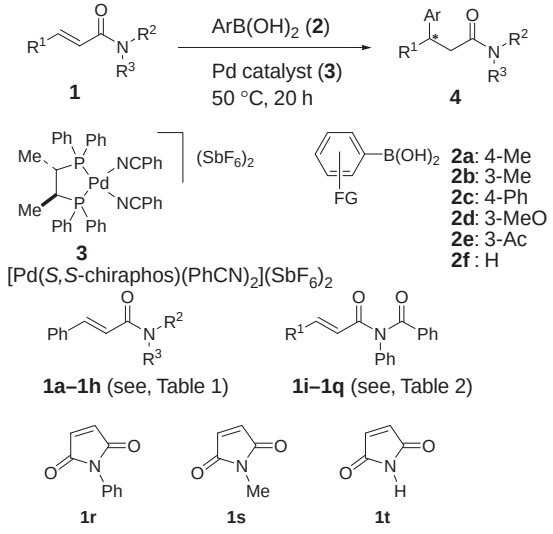
Palladium-catalyzed 1,4-addition of arylboronic acids to unsaturated carbonyl compounds has been limitedly used for ketone and aldehyde derivatives. It was found that reaction with *N*-acylamides exceptionally proceeds with high yields and high enantioselectivities. A dicationic palladium–chiraphos catalyst **3** gave optically active β-arylamides of up to 98% ee.

Conjugate addition of organometallic compounds to electron-deficient alkenes is one of the widely used methods for construction of stereodefined C–C bonds. Since it is key steps in various syntheses of biologically active compounds, tremendous efforts have been devoted to the development of asymmetric variants of this protocol.[1] We have reported that aryl- and 1-alkenylboronic acids smoothly undergo 1,4-addition to α,β-unsaturated carbonyl compounds in the presence of a rhodium(I)[2] or dicationic palladium(II) catalyst.[3] These reactions were extended to asymmetric reactions giving optically active carbonyl compounds possessing a chiral center at the β-carbon.[4] Although rhodium catalysts have a broad scope for cyclic and acyclic α,β-unsaturated ketones, esters, amides, phosphonates, and nitro compounds, palladium catalysts[5–7] have been limitedly used for unsaturated ketones and aldehydes since the reaction with unsaturated acid derivatives results in formation of Heck products with precipitating palladium-black. We report here the first 1,4-addition to unsaturated acid derivatives catalyzed by palladium complexes (Scheme 1).



Scheme 1. Asymmetric 1,4-addition of $ArB(OH)_2$ to unsaturated *N*-acyl amides catalyzed by a dicationic palladium(II) catalyst.

The addition to electron-deficient *N*-acylamides **1** with a palladium–chiraphos catalyst **3** provided optically active β-arylamides **4** of up to 98% ee. The yields and enantioselectivities in 1,4-addition of *p*-tolylboronic acid (**2**) to N-substituted *trans*-cinnamamides **1** with $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (1 mol %) (**3**) are summarized in Table 1. No reaction was observed for *N*-phenyl amide **1a** even at elevated temperature (Entry 1), but various *N*-acyl amides afforded desired 1,4-addition products without accompanying Heck products in the presence of 1.5 equivalents of boronic acid. The use of bulky *N*-benzoyl amide **1c** resulted in a higher yield and higher enantioselectivity (89%, 85% ee) than those in the case of smaller *N*-acetyl amide **1b** (42%, 77% ee) (Entries 2 and 3). Increase in the bulkiness of the *N*-benzoyl group by methyl substitution of meta (**1d**) or ortho carbon (**1e**) was not effective for improving the selectivity (Entries 4 and 5, 85–86% ee). However, the enantioselectivities were increased to over 96% by further increasing the bulkiness of the amide group by N-substitution with a methyl (**1h**) or phenyl group (**1i**) (Entries 6–9). The yields exceeded 70% when 3 equivalents of boronic acid were used in aqueous THF or DMF (Entries 11 and 12). The 1,4-addition product obtained from **2a** and **1i** (Entry 11) was treated with H_2SO_4 in MeOH to produce methyl 3-phenyl-3-tolylpropanoate, ($[\alpha]_D = +2.5°$ (*c* 0.10, $CHCl_3$). The absolute configuration was determined to be S by a comparison of reported specific rotation; lit.[8] 97% ee (R), $[\alpha]_D = -2.7°$ (*c* 0.72, $CHCl_3$).

The catalytic cycle involves insertion of alkene into the C–Pd bond to give *C*-enolate, which is in equilibrium with

Table 1. Reaction conditions[a]

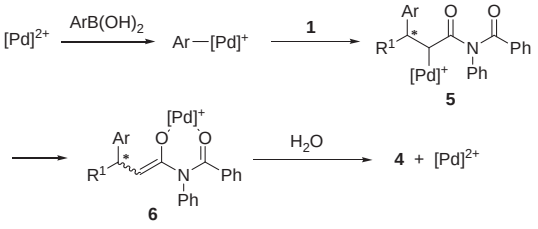
Entry	**1** (R^1 = Ph)			Solvent	Yield /%	%ee
	R^2	R^3				
1	H	Ph	**1a**	Acetone	0	—
2	H	COMe	**1b**	Acetone	42	77
3	H	COPh	**1c**	Acetone	89	85
4	H	CO(3-MePh)	**1d**	Acetone	66	86
5	H	CO(2-MePh)	**1e**	Acetone	65	85
6	Me	COMe	**1f**	Acetone	14	—
7	Ph	COMe	**1g**	Acetone	18	—
8	Me	COPh	**1h**	Acetone	32	96
9	Ph	COPh	**1i**	Acetone	43	98
10	Ph	COPh	**1i**	THF	48	98
11[b]	Ph	COPh	**1i**	THF	75	98
12[b,c]	Ph	COPh	**1i**	DMF	72	96

[a]A mixture of unsaturated amide (0.5 mmol), *p*-tolylboronic acid (**2a**, 0.75 mmol) and Pd catalyst (**3**, 1 mol %) in solvent/water (2 mL/0.2 mL) was stirred at 20 °C for 20 h. Yields determined by ^1H NMR. [b]3 equivalents of boronic acid was used. [c]At 50 °C.

Table 2. Asymmetric 1,4-addition of arylboronic acids to unsaturated *N*-benzoyl amides[a]

Entry	**1R**[1] (R^2 = Ph,R^3 = COPh)		**2**, FG		Solvent	Temp/°C	Yield/%[b]	%ee
1	Ph	**1i**	3-Me	**2b**	DMF–H_2O	50	88 (86)	94[c]
2	Ph	**1i**	3-MeO	**2d**	DMF–H_2O	50	74	98
3	Ph	**1i**	3-MeCO	**2e**	THF–H_2O	50	60	96
4	2-MeOPh	**1j**	3-Me	**2b**	DMF–H_2O	50	80 (76)	98
5	2-MeOPh	**1j**	H	**2f**	DMF–H_2O	50	75 (70)	96
6	3-MeOPh	**1k**	3-Me	**2b**	DMF–H_2O	50	74 (73)	95
7	3-MeOPh	**1k**	H	**2f**	DMF–H_2O	50	76 (76)	96
8	3-MeOPh	**1k**	4-Ph	**2c**	DMF–H_2O	50	70	97
9	4-MeOPh	**1l**	3-Me	**2b**	DMF–H_2O	50	73 (70)	95[c]
10	4-MeOPh	**1l**	H	**2f**	DMF–H_2O	50	71 (69)	93
11	2,3-$(MeO)_2$Ph	**1m**	3-Me	**2b**	DMF–H_2O	50	88 (83)	96
12	2,3-$(MeO)_2$Ph	**1m**	H	**2f**	DMF–H_2O	50	82 (80)	95
13	Me	**1n**	3-MeO	**2d**	THF–H_2O	25	(96)	92
14	*n*-C_3H_7	**1o**	3-MeO	**2d**	THF–H_2O	25	77	90
15[d]	*n*-C_5H_{11}	**1p**	3-MeO	**2d**	THF–H_2O	50	84 (80)	92
16[d]	$(CH_3)_2CH$	**1q**	3-MeO	**2d**	THF–H_2O	50	60	90
17	—	**1r**	3-MeO	**2d**	DMF–H_2O	35	99 (92)	40
18	—	**1s**	3-MeO	**2d**	THF–H_2O	35	92	90
19	—	**1t**	3-MeO	**2d**	THF–H_2O	35	96	90

[a]A mixture of unsaturated amide (**1**, 0.5 mmol), arylboronic acid (**2**, 1.5 mmol), and Pd catalyst (**3**, 1 mol %) in DMF/water (2 mL/0.2 mL) was stirred for 20 h. [b]NMR yields and isolated yields are shown in parentheses. [c]ee was determined after a deprotection of amide. [d]5 mol % of Pd catalyst was used.



Scheme 2. Catalytic cycle.

water-sensitive *O*-enolate when enones and enals are used as the substrate. However, *C*-enolates generated from unsaturated esters and typical amides are led to the Heck coupling product via β-elimination because of slow migration of *C*-enolate to *O*-one. Thus, the role of the *N*-acyl group can be its chelating ability to the cationic palladium(II) species for migration to *O*-enolate **6** and its hydrolysis with water. (Scheme 2). Another role of the *N*-acyl group can be attributable to its electron-withdrawing property to accelerate the insertion of **1** into the C–Pd bond.

Enantioselective additions to *N*-benzoyl-*N*-phenyl-2-alkenamides (**1a**–**1q**, R^1 = aryl and alkyl, R^2 = Ph, R^3 = COPh) or maleimides (**1r**–**1t**) are summarized in Table 2. (*E*)-Cinnamamide and its derivatives possessing one or two methoxy substituents on the aromatic ring easily achieved high enantioselectivities ranging from 93 to 98% ee (Entries 1–12), which are comparable to those obtained for β-arylenones with the same palladium–chiraphos catalyst **3**.[6h] Aliphatic amides (**1n**–**1q**) resulted in 90–92% ee (Entries 13–16), which were 7 to 10% higher than those of the corresponding enones or enals[6b,6i] possessing a methyl, propyl, pentyl, and isopropyl group at the β-carbon. Cyclic imides such as maleimide (**1t**) and *N*-methylmaleimide (**1s**) resulted in higher enantioselectivities than that in the case of *N*-phenyl derivative **1r** (Entries 17–19).

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