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Asymmetric 1,4-addition of triarylbismuths to enones catalyzed by dicationic palladium(II) complexes

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A 1,4-addition of triarylbismuths to cyclic and acyclic enones was carried out in aqueous methanol in the presence of a chiral phosphine–dicationic palladium(II) complex. Palladium complexes of (*S*,*S*)-chiraphos or (*S*,*S*)-dipamp gave optically active β-arylketones of up to 95% ee.

In recent years we have been exploring metal-catalyzed 1,4-addition reactions of organoboron compounds, and in the process we have reported a very general catalytic cycle for 1,4-addition of aryl- and 1-alkenylboronic acids to α,β-unsaturated carbonyl compounds with rhodium(I) complexes.[1,2] The protocol has a quite high level of generality, enabling exploration of analogous addition reactions of organosilicon,[3] -bismuth,[4] -tin,[5] -titanium,[6] -zirconium,[7] and -zinc[8] compounds and their asymmetric versions using chiral phosphine–rhodium(I) complexes.[9] Dicationic palladium(II) complexes also are excellent catalysts for 1,4-additions of arylboronic acids[10] and arylsiloxanes[11] to enones in aqueous media *via* a catalytic cycle analogous to that of rhodium complexes. Although the use of arylbismuths in such metal-catalyzed reactions is rare, they have promising potential due to the simplicity of their preparation, isolation and handling as well as their functional group compatibility.[12] In this report, we describe an asymmetric palladium(II)-catalyzed 1,4-addition reaction of triarylbismuths to enones (Scheme 1). The reaction provided optically active β-arylketones (**4**) of up to 95% ee in the presence of a chiraphos- or dipamp–cationic palladium(II) catalyst (**3**).

At the outset, dicationic palladium(II) catalysts were screened to carry out 1,4-addition of Ph_3Bi to 2-cyclohexenone in MeOH–H_2O (6 : 1) (Table 1). $[Pd(dppe)(PhCN)_2](BF_4)_2$ stabilized by two benzonitriles resulted in 27% yield with an accompanying biphenyl derived by double transmetalation to the catalyst (entry 1). Addition of $Cu(BF_4)_2$ to $[Pd(dppe)(PhCN)_2](BF_4)_2$ or $PdCl_2$(dppe) provided an active catalyst, resulting in 90% yields at room temperature *via in situ* generation of a highly electrophilic nitrile-free complex (entries 2 and 3). Another role of the copper salt is reoxidation of palladium(0) species by double transmetalation giving biphenyl. Under the conditions used, 2–2.8 of the three phenyl groups on the bismuth atom were added to the enone without any difficulty. Such high catalyst efficiency is specific for bisphosphines bridged by two carbon atoms since the catalysts possessing a dppm (0%), dppp (27%), dppb (0%) or binap (0%) ligand resulted in almost no product, as was observed in related reactions of arylboronic acids and arylsiloxanes. Thus, palladium complexes of dipamp (**3a**, **3b**), chiraphos (**3c**), norphos (**3d**), and 1,1′-binaphthol-based diphosphonite (**3e**) are catalysts that meet this requirement (entries 4–10). Of the two methods for *in situ* preparation of nitrile-free catalysts, the ligand exchange between **3b** and $Cu(BF_4)_2$ was more favorable for the asymmetric version than that between **3a** and $Cu(BF_4)_2$ because the former easily takes place at temperatures lower than 0 °C (entries 4–7). The absolute configuration of 3-phenylcyclohexanone obtained from an (*S*,*S*)-dipamp complex (**3b**) was *R*, and enantioselectivity was increased by decreasing the reaction temperature. An (*S*,*S*)-chiraphos catalyst (**3c**) resulted in an *S* isomer with 12% ee (entry 8), though it is an excellent catalyst for 2-cyclopentenone and acyclic enones, as shown in Table 2. Palladium complexes of rigid norphos (**3d**) did not catalyze the reaction, presumably due to its large bite angle compared to that of

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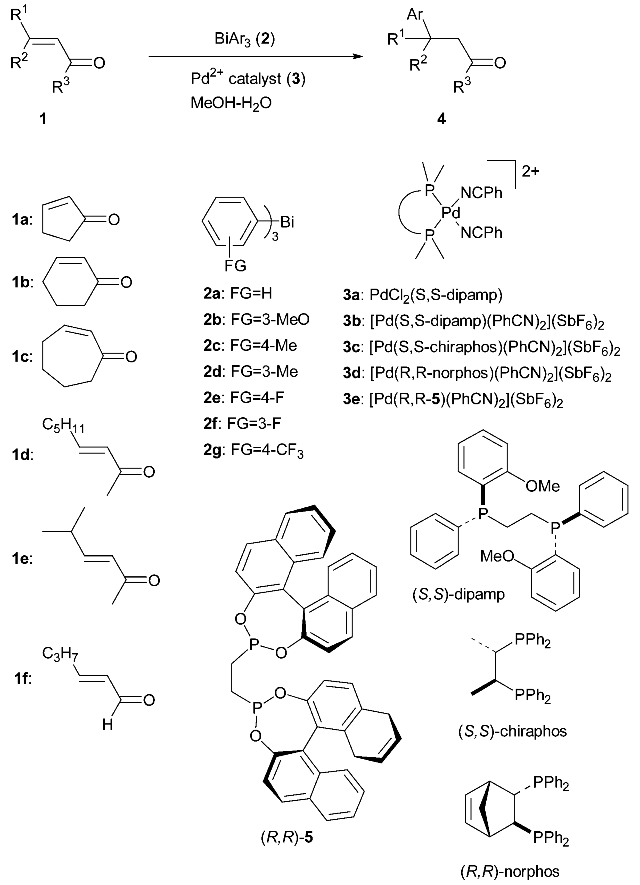

Scheme 1 Asymmetric addition of Ar_3Bi to enones catalyzed by dicationic palladium(II) catalysts.

Table 1 Effect of catalysts in the addition of Ar_3Bi to 2-cyclohexenone[a]

Entry	Catalyst	Temp./ °C	Yield (%)	% ee
1	$[Pd(dppe)(PhCN)_2](BF_4)_2$	20	27[b]	—
2	$[Pd(dppe)(PhCN)_2](BF_4)_2/Cu(BF_4)_2$	20	90[b]	—
3	$PdCl_2(dppe)/Cu(BF_4)_2$	20	90[b]	—
4	**3a**/$Cu(BF_4)_2$	20	99	86 (*R*)
5	**3a**/$Cu(BF_4)_2$	0	trace	—
6	**3b**/$Cu(BF_4)_2$	0	94	89 (*R*)
7	**3b**/$Cu(BF_4)_2$	−5	92	92 (*R*)
8	**3c**/$Cu(BF_4)_2$	−5	89	12 (*S*)
9	**3d**/$Cu(BF_4)_2$	20	trace	
10	**3e**/$Cu(BF_4)_2$	20	trace	

[a] A mixture of 2-cyclohexenone (1 mmol), Ph_3Bi (0.6 mmol) in MeOH (6 ml) and H_2O (1 ml) was stirred at room temperature for 21 h in the presence of a palladium complex (4 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (if used, 0.76 mmol). [b] Reactions were accompanied by biphenyl (18–24%).

flexible dppe analogues (entry 9). The reaction also failed when bisphosphonite (*R*,*R*-**5**)[2f] was used (entry 10).

Asymmetric 1,4-additions of representative triarylbismuths to enones in aqueous methanol are summarized in Table 2.† The enantioselectivity depends on the combination between a chiral ligand and a carbonyl compound. Chiraphos was found to be the best ligand for 2-cyclopentenone (**1a**), resulting in 90–95% ee for Ph_3Bi (**2a**), $(3\text{-}MeOPh)_3Bi$ (**2b**), and $(3\text{-}MePh)_3Bi$ (**2d**) (entries 1–4). In contrast, dipamp gave much better selectivities than those of chiraphos for 2-cyclohexenone (**1b**) (entries 5 and 6), giving 74–94% ee for Ph_3Bi (**2a**), $(4\text{-}MePh)_3Bi$ (**2c**), $(3\text{-}MeOPh)_3Bi$ (**2b**), $(3\text{-}MePh)_3Bi$ (**2d**), $(4\text{-}FPh)_3Bi$ (**2e**), $(3\text{-}FPh)_3Bi$ (**2f**), and $(4\text{-}CF_3Ph)_3Bi$ (**2g**) (entries 6–12). Among them, two *para*-substituted derivatives (**2c** and **2g**) unexpectedly resulted in 74% ee and 84% ee for an unknown reason, whereas other *para*- and *meta*-substituted arylbismuths easily resulted in over 90% ee. 2-Cycloheptenone (**1c**) resulted in 76% ee with dipamp and 51% ee with chiraphos, but all attempts at selective addition achieving more than 90% ee were unsuccessful (entries 13 and 14). Chiraphos was a better ligand than dipamp for acyclic enones or enals that have a *trans* olefin geometry. The steric bulkiness of a β-substituent of 5-methyl-3-hexen-2-one (**1e**, 81–89% ee) afforded slightly better enantioselectivities than those of 3-nonen-2-one (**1d**, 80–84% ee) (entries 16–21). Addition to enals such as 2-hexenal (**1f**) was very slow due to formation of hemiacetal in aqueous solution and resulted in a moderate range of enantioselectivities (entry 22).

The reaction may proceed through transmetalation of Ar_3Bi to a dicationic palladium(II) complex giving Ar–[Pd]$^+$, insertion of an enone into the C–Pd bond, and hydrolysis of the resulting palladium enolate with water. Judging from the reaction temperatures employed as reaction conditions to achieve more than 90% yields,[10,11] the rate of transmetalation was in the order of Ph_3Bi (−5 °C) > $ArB(OH)_2$ (20 °C) > $ArSi(OMe)_3$ (75 °C). Work aimed at characterization of the chiral phosphine–arylpalladium(II) intermediate obtained by transmetalation is in progress to elucidate the asymmetric induction mechanism.

Table 2 Asymmetric addition of Ar_3Bi to enones[a]

Entry	Enone	Ar_3Bi	Catalyst	Temp./ °C	Yield (%)[b]	% ee[c]
1	**1a**	**2a**	**3b**	−5	49	42
2	**1a**	**2a**	**3c**	−5	85	95
3	**1a**	**2b**	**3c**	5	84	92
4	**1a**	**2d**	**3c**	−5	94	92
5	**1b**	**2a**	**3c**	−5	62	12
6	**1b**	**2a**	**3b**	−5	92	92
7	**1b**	**2b**	**3b**	10	92	93
8	**1b**	**2c**	**3b**	−5	64	74
9	**1b**	**2d**	**3b**	−5	98	92
10	**1b**	**2e**	**3b**	10	93	90
11	**1b**	**2f**	**3b**	10	93	94
12[d]	**1b**	**2g**	**3b**	10	66	84
13	**1c**	**2a**	**3b**	−5	89	76
14	**1c**	**2a**	**3c**	−5	89	51
15	**1d**	**2a**	**3b**	−5	72	26
16	**1d**	**2a**	**3c**	−5	99	83
17	**1d**	**2b**	**3c**	5	85	84
18	**1d**	**2f**	**3c**	−5	76	80
19	**1e**	**2a**	**3c**	−5	63	85
20	**1e**	**2b**	**3c**	10	70	89
21	**1e**	**2f**	**3c**	10	31	81
22	**1f**	**2a**	**3c**	−5	55	68

[a] A mixture of enone (1 mmol), Ar_3Bi (0.6 mmol) in MeOH (6 ml) and H_2O (1 ml) was stirred for 21 h in the presence of a palladium catalyst (**3**, 4 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (0.76 mmol). [b] Isolated yields by column chromatography. [c] Enantiomeric excess was determined by a chiral stationary column. [d] The reaction was conducted in MeOH without using water.

Notes and references

† *Typical experimental procedure (Table 2, entry 6).* Ph_3Bi (0.6 mmol), $Cu(BF_4)_2{\cdot}6H_2O$ (0.76 mmol), methanol (6 ml), 2-cyclohexenone (1 mmol) and water (1 ml) were added to a flask under nitrogen. Finally, [Pd(*S*,*S*-dipamp)$(PhCN)_2$]$(SbF_6)_2$ (0.04 mmol) was added at −5 °C. After being stirred for 21 h, chromatography on silica gel gave (*R*)-3-phenylcyclohexanone in 92% yield. The enantiomer excess (92% ee) was determined by HPLC analysis using Daicel Chiralpak AD (hexane/2-propanol = 98 : 2).

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