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Application of Dicyclohexyl-(*S*)-trimethoxyphenyl Phosphine·HBF_4 Salt for the Highly Selective Suzuki Coupling of the C−Cl Bond in β-Chlorobutenolides Over the More Reactive Allylic C−O Bond

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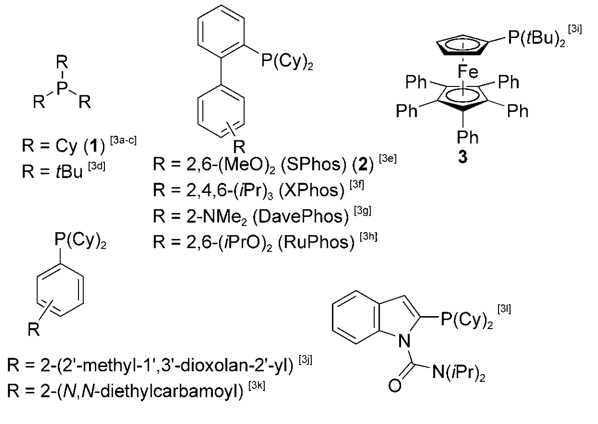
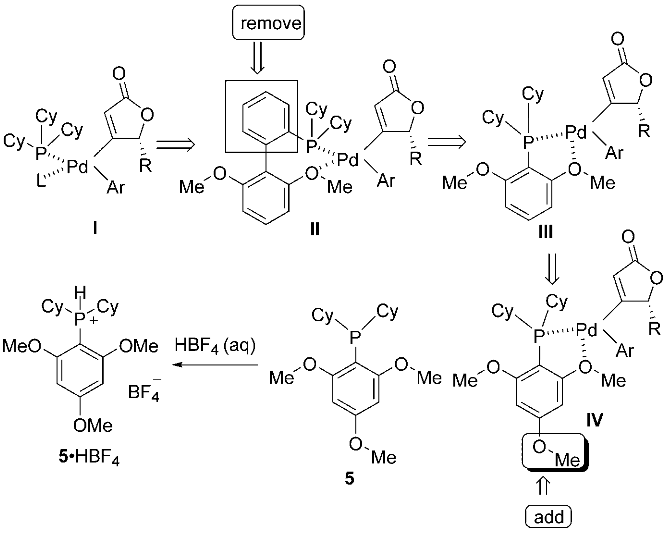
In memory of Professor Xian Huang

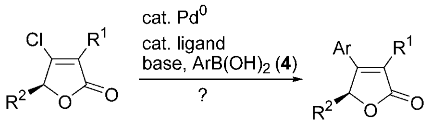
The reactions of C−Cl bonds are currently of interest due to the cheap, readily available nature of organic chlorides and the atom economy caused by the low atomic weight of the chlorine atom compared with reactions involving C−Br and C−I bonds.[1] Much attention has been paid to research in this area.[2] It has been well established that electron-rich, sterically bulky phosphines may serve nicely as ligands in the Suzuki coupling reactions of organic chlorides. Some of the most notable ligands (including compounds **1**–**3**; Cy = cyclohexyl) in this area are shown here.[3]



In 2001, we developed an efficient method to synthesize optically active β-chlorobutenolides from 2,3-allenoic acid–chiral base salts using $CuCl_2$ as the halogen source.[4] In this type of compound, due to the presence of the reactive lactonic, allylic C−O bond, it is a challenge to couple the relatively inert C−Cl bond exclusively with the organic boronic acid (**4**) over the more reactive allylic C−O bond also present [Eq. (1)].[5] In this paper, we wish to report the application of a new ligand **5**, prepared in this group, to this reaction (Scheme 1); the C−Cl bond is efficiently cleaved in the presence of Pd, while the more reactive allylic C−O bond remains unchanged.



Scheme 1. Rationale for a new ligand.



(1)

We began by screening reaction conditions using the commercially available and well established ligands PCy_3 (**1**), by

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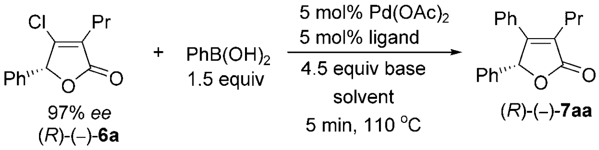
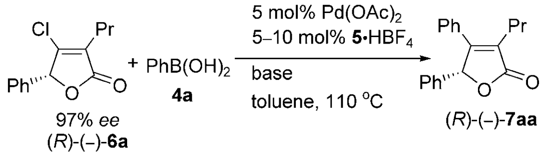
Table 1. $Pd(OAc)_2$-$Cy_3P{\cdot}HBF_4$- or -SPhos-catalyzed Suzuki coupling of (*R*)-(−)-**6a** with $PhB(OH)_2$ to form (*R*)-(−)-**7aa**.



Entry	Ligand	Base	Solvent	Yield [%]	*ee* [%]	Recovery of **6a** [%]
1	**1**·HBF_4[a]	K_2CO_3	DMF	trace	–	–
2	**1**·HBF_4[a]	K_2CO_3	dioxane	38	42	32
3	**1**·HBF_4	K_3PO_4	toluene	38	16	25
4	**1**·HBF_4	Et_3N	toluene	5	44	64
5	**1**·HBF_4[b]	K_2CO_3	toluene	68	88	29
6	**1**·HBF_4[b,c]	K_2CO_3	toluene	67	0	9
7	**2**	K_2CO_3	DMF	5	–	6
8	**2**	K_2CO_3	dioxane	18	–	26
9	**2**	K_3PO_4	toluene	69	66	10
10	**2**	Et_3N	toluene	6	–	86
11	**2**[b]	K_2CO_3	toluene	17	92	84
12	**2**[b,c]	K_2CO_3	toluene	40	–[d]	11

[a] Reaction time 30 min. [b] 10 mol% of this ligand was used. [c] Reaction time: 60 min. [d] Low *ee*. The exact *ee* value is not available since the purity was only 83%.

Table 2. $Pd(OAc)_2$/**5**-catalyzed Suzuki coupling of (*R*)-(−)-**6a** with $PhB(OH)_2$ to form (*R*)-(−)-**7aa**.



Entry	$PhB(OH)_2$ [equiv]	**5**·HBF_4 [%]	Base [equiv]	*t* [min]	Yield [%]	*ee* [%]
1	1.5	5	K_3PO_4 (3.5)	5	32[a]	74
2	1.5	5	K_3PO_3 (3.5)[b]	5	65[c]	60
3[d]	2.0	6	K_2CO_3 (3.5)	30	81	0
4	2.0	10	K_2CO_3 (3.5)	30	100	35
5	2.0	10	K_2CO_3 (4.5)	5	86	88
6	2.0	5	K_2CO_3 (4.5)	5	83	94
7	1.5	5	K_2CO_3 (3.5)	5	77[e]	90
8	1.5	10	K_2CO_3 (4.5)	5	65[f]	85
9	1.5	5	K_2CO_3 (4.5)	5	75	98

[a] 36% of **6a** was recovered. [b] 1.0 equiv of H_2O was added. [c] 13% of **6a** was recovered. [d] 3 mol% of $Pd(OAc)_2$ was added. [e] 22% of **6a** was recovered. [f] 15% of **6a** was recovered.

Shen et al.[3a] and Fu et al.,[3b,c] and SPhos (**2**), by Buchwald et al.[3e] (Table 1). As shown in Table 1, a slow reaction with considerable racemization is the major challenge we needed to tackle. By comparing the results of using PCy_3 as the ligand with those of SPhos (entries 3 and 9, Table 1) we concluded that the presence of a methoxy group in SPhos may promote the C−Cl coupling reaction through a faster reductive elimination reaction and retard the oxidative addition of Pd to the allylic C−O bond due to the increased steric hindrance in **II** compared with **I** (see Scheme 1).[6] Thus, we reasoned that removing the phenyl group connecting the phosphorous atom with the 2,6-dimethoxyphenyl group in **II** may create a much better ligand for this transformation due to the further increase in steric hindrance caused by the more favorable formation of a five-membered ring coordination complex in **III** as compared with the seven-membered ring coordination in **II**.[6]

Based on this notion, and in order to use the cheaper *S*-trimethoxybenzene as the starting material for the synthesis, ligand **5** was designed and prepared.[7] Compound **5** was formed by the lithiation of *S*-trimethoxybenzene to generate 2,4,6-trimethoxyphenyl lithium, which was then treated with Cy_2PCl, generated in situ from the reaction of cyclohexyl magnesium chloride with PCl_3, to afford dicyclohexyl(2,4,6-trimethoxyphenyl)phosphine (**5**). This compound was treated with aqueous HBF_4, as previously reported by Fu et al.,[8] to afford the air-stable solid salt **5**·HBF_4 for further study.

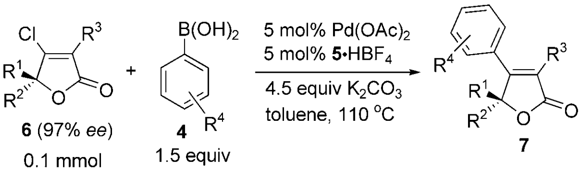
Luckily, (*R*)-(−)-4-chloro-5-phenyl-3-propylfuran-2(5*H*)-one, (*R*)-(−)-**6a**, did undergo the $Pd(OAc)_2$/**5**-catalyzed Suzuki coupling reaction with phenylboronic acid (**4a**) in toluene, with K_3PO_4 as the base to give product (*R*)-**7aa** in an improved *ee* (74%), albeit with low conversion (entry 1, Table 2); the addition of one equivalent of water afforded the product in a higher yield but with lower *ee* (entry 2, Table 2). Further study led to the observation that by performing the reaction in toluene using 3.5 equivalents of K_2CO_3 as the base affords the product (*R*)-(−)-**7aa** in 100% yield, but only 35% *ee* (entry 4, Table 2). We reasoned that increasing the loading of K_2CO_3 might speed up the transmetallation process and ensure a faster coupling reaction.[9] Thus, through further screening, we were able to find a transformation without racemization that gives (*R*)-(−)-**7aa** in 75% yield and 98% *ee* by using 1.5 equivalents of $PhB(OH)_2$ and 5 mol% **5**·HBF_4 (entry 9, Table 2). As a comparison, it should be noted that, if the reaction is performed with $PCy_3{\cdot}HBF_4$[3a–c] or SPhos[3e] as the ligand under the same reaction conditions (entries 6 and 12, Table 1), the essentially racemized product **7aa** is produced with some (*R*)-(−)-**6a** remaining.

Encouraged by these results, we investigated the scope of this highly selective coupling reaction of optically active β-chlorobutenolides for our newly developed Suzuki coupling conditions (Table 3). In all the cases tried, the C−Cl bond Suzuki coupling reaction afforded the optically active β-substituted butenolides without touching the reactive, allylic C−O bond.

We also performed a control experiment to show that treating the coupling product (*S*)-(+)-**7aa** (98% *ee*) with SPhos (**2**) does not cause racemization; however, under the standard conditions with **2** as the ligand, not only racemization occurs, indicating that the allylic C−O bond has been easily cleaved in the presence of Pd and SPhos,[5] but also a new, unidentified product is formed (Scheme 2).

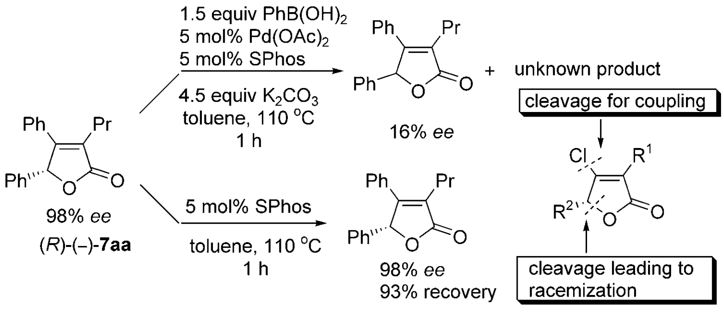
In conclusion, we have successfully applied the HBF_4 salt of dicyclohexyl(2,4,6-trimethoxyphenyl)phosphine to the highly selective activation of the relatively inert C−Cl bond in β-chlorobutenolides over the more reactive lactonic, allylic C−O bond, which may be explained by the electronic and

Table 3. Suzuki coupling reactions of (*S*)-(−)-**6** and **4** using **5** as the ligand.



Entry	R^1	R^2	R^3	**6**	R^4	**4**	*t* [min]	Isolated yield [%]	Product	*ee* [%]
1	Ph	H	Me	(*S*)-(+)-**6b**	H	**4a**	6	83	(*S*)-(+)-**7ba**	99
2	Ph	H	Me	(*S*)-(+)-**6b**	4-MeO	**4b**	6	100	(*S*)-(+)-**7bb**	97
3	Ph	H	Me	(*S*)-(+)-**6b**	4-Me	**4c**	5	72	(*S*)-(+)-**7bc**	96
4	H	$n\mathrm{C}_5\mathrm{H}_{11}$	Me	(*R*)-(+)-**6c**	H	**4a**	10	81	(*R*)-(−)-**7ca**	97
5[a]	H	$n\mathrm{C}_5\mathrm{H}_{11}$	Me	(*R*)-(+)-**6c**	4-MeO	**4b**	10	93	(*R*)-(−)-**7cb**	97
6[a]	H	$n\mathrm{C}_5\mathrm{H}_{11}$	Me	(*R*)-(+)-**6c**	4-Me	**4c**	10	81	(*R*)-(−)-**7cc**	98
7[a]	H	$n\mathrm{C}_5\mathrm{H}_{11}$	Me	(*R*)-(+)-**6c**	3-MeO	**4d**	10	84	(*R*)-(−)-**7 cd**	98
8	H	Ph	Pr	(*R*)-(−)-**6a**	3-MeO	**4d**	5	90	(*R*)-(−)-**7ad**	95
9	H	Ph	Pr	(*R*)-(−)-**6a**	H	**4a**	5	75	(*R*)-(−)-**7aa**	98
10[b]	H	Ph	Pr	(*R*)-(−)-**6a**	H	**4a**	8	84	(*R*)-(−)-**7aa**	98

[a] 2.0 equivalents of $PhB(OH)_2$ were used; with 1.5 equivalents of $PhB(OH)_2$ and the reaction did not go to completion. [b] The reaction was conducted with 0.98 mmol of (*R*)-(−)-**6a**.



Scheme 2. Reaction of (*R*)-(−)-**7aa** and speculation about its racemization.

steric effects shown in Scheme 1. The HBF_4 salt of this ligand is easy to prepare and air stable. Further studies in this area of this ligand are being conducted in our laboratory.

Experimental Section

Typical procedure for the preparation of (*R*)-(−)-4,5-diphenyl-3-propylfuran-2(5*H*)-one, (*R*)-(−)-7aa: $Pd(OAc)_2$ (1.2 mg, 0.0054 mmol), **5**·HBF_4 (2.3 mg, 0.0051 mmol), K_2CO_3 (63.1 mg, 0.46 mmol), **4a** (19.1 mg, 98% purity, 0.15 mmol) and toluene (0.5 mL) were sequentially added to a flame-dried, nitrogen filled Schlenk vessel. After being stirred for about 3 min at room temperature, (*R*)-(−)-**6a** (22.8 mg, 0.096 mmol, 97% *ee*) and toluene (0.5 mL) were added. The resulting mixture was heated at 110 °C, by using a preheated oil bath, for 6 min (until complete conversation, as monitored by TLC) and then quenched with water (10 mL), extracted with diethyl ether (2×10 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Filtration, evaporation, and purification by column chromatography (petroleum ether/ethyl acetate = 10:1) on silica gel afforded (*R*)-(−)-**7aa** (20.1 mg, 75%) as a white solid in 98% *ee*, as determined by HPLC (Chiralpak OD-H, *n*-hexane/*i*PrOH = 65:35, 0.8 mL min^{-1}, $\lambda = 230$ nm, $t_R = 8.3$ (major), 6.3 min (minor)). $[\alpha]_D^{20} = -152.0$ ($c = 0.95$, $CHCl_3$); m.p.: 103.8–104.9 °C (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$–7.15 (m, 10 H), 6.14 (s, 1 H), 2.58–2.42 (m, 2 H), 1.78–1.60 (m, 2 H), 0.98 ppm (t, $J = 7.4$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.1$, 159.1, 134.9, 131.5, 129.5, 129.1, 128.7, 128.5, 127.8, 127.3, 83.7, 26.3, 21.5, 14.1 ppm; IR (KBr): $\tilde{\nu} = 3057$, 3027, 2958, 2939, 2870, 1749, 1734, 1649, 1498, 1455, 1445, 1355, 1340, 1206, 1126, 1090, 1072, 1014 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 279 (16.57) $[M+1]^+$, 278 (77.10) $[M]^+$, 173 (100); elemental analysis calcd (%) for $C_{19}H_{18}O_2$: C 81.99, H 6.52; found: C 82.00, H 6.53.

Acknowledgements

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Keywords: chlorine · palladium · selectivity · Suzuki coupling reactions

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