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Rhodium-catalyzed addition of aryl boronic acids to 1,2-diketones and 1,2-ketoesters

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Abstract—The metal complex $Rh(acac)(CO)_2$ in the presence of dicyclohexylphenylphosphine provides a useful catalyst system for the addition of boronic acids to 1,2-diketones and 1,2-ketoesters. The best yields were obtained when the transformation was performed in DME/H_2O at 80 °C with 4 equiv of the boronic acid. The results discussed herein extend the scope of the addition of arylboronic acids to highly activated diketones and ketoesters. The products of the reaction are useful in the synthesis of natural products containing oxygenation next to esters or ketones.

The addition of carbon nucleophiles to 1,2-diketones and 1,2-ketoesters is an attractive method for the synthesis of tertiary alcohols vicinal to a carbonyl group.[1] The tertiary alcohols of this type are useful precursors for niacin receptor agonists based on acifan[2,3] and the HIV integrase inhibitor integrastatin.[4] While auxiliary based methods exist for the asymmetric synthesis of such derivatives,[5,6] until recently no catalytic asymmetric methods provided these products. Catalytic methods for the direct addition of aryl groups have been limited to Friedel–Crafts reactions[7] and the rhodium-catalyzed addition of arylstannanes.[8] While these methods provide excellent yields, the limitation of the Friedel–Crafts reaction to electron rich aromatics and the toxicity of stannanes represent significant drawbacks. The recent extension of rhodium-catalyzed nucleophilic additions of arylboronic acids[9–11] to trifluoromethyl ketones,[12] isatin derivatives,[13,14] and oxalates[15] shows that the activation of the carbon–boron bond may provide a useful solution to the problems associated with stannanes and Friedel–Crafts reactions.[16] These reactions also provide a useful alternative to Grignard reactions as they can be performed in the presence of water with only a small amount of transition metal catalyst.

While excellent results have been obtained with isatin derivatives and aryl trifluoromethyl ketones, the carbonyls in these substrates cannot enolize as they possess no acidic α-protons. Previous studies have shown that enolizable 1,2-diketones and 1,2-ketoesters are more challenging electrophiles.[17,18] These substrates can polymerize rapidly if conditions are highly acidic or basic, leading to problems with conversion. The adaptation of the conditions used for the rhodium-catalyzed addition of arylboronic acids to aldehydes[11,19–21] provides a starting point for the development of an asymmetric version of this reaction.

Initial attempts to affect this transformation focused on the addition of phenylboronic acid (**1**) to 2,3-butanedione (**2**) using $Rh(acac)(CO)_2$ as a precatalyst in the presence of 1,1′-bis(diphenylphosphino)ferrocene (dppf, **4**) (Table 1). Ligands with large P–Rh–P angles have been reported to accelerate the addition reaction with aldehyde substrates.[11] While the product was formed from this addition, the yield of the process was only 17%. Rhodium-catalyzed addition reactions are known to be sensitive to both the steric and the electronic properties of the phosphine ligands,[18] so the variation of the phosphine structure was undertaken in order to improve the reaction. The use of triarylphosphines only provided low yields of the desired addition product (Table 1, entries 2–5). Switching to trialkylphosphines proved to be more advantageous. Tri(*t*-butyl) phosphine has been shown to provide superior yields with faster reaction rates when similar rhodium-catalyzed reactions were performed with aldehydes.[19] Using tri-*t*-butyl phosphine (**10**) as a ligand, the yield of the reaction increased to

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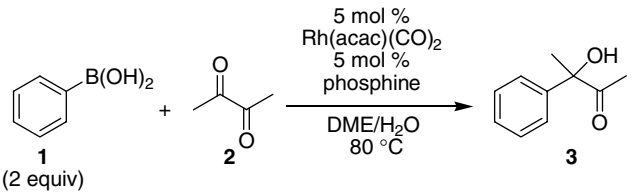
Table 1. Screen of phosphine ligands



Entry	Phosphine	Yield (%)
1	dppf (**4**)	17
2	Triphenylphosphine (**5**)	17
3	Tris(*p*-methoxy)phosphine (**6**)	17
4	Tris(*p*-fluorophenyl)phosphine (**7**)	7
5	Tri-2-furylphosphine (**8**)	2
6	Tributylphosphine (**9**)	Trace
7	Tri(*t*-butyl)phosphine (**10**)	26
8	Di(*t*-butyl)phenylphosphine (**11**)	30
9	2-(Di-*t*-butylphosphino)biphenyl (**12**)	Trace
10	Tricyclohexylphosphine (**13**)	0
11	Dicyclohexylphenylphosphine (**14**)	61
12	2-(Dicyclohexylphosphino)biphenyl (**15**)	Trace

26% (Table 1, entry 7). The use of other trialkyl phosphines also gave low yields. Mixed alkyl/aryl substituted phosphines showed little improvement except for dicyclohexylphenylphosphine (**14**) which gave an encouraging 61% yield.

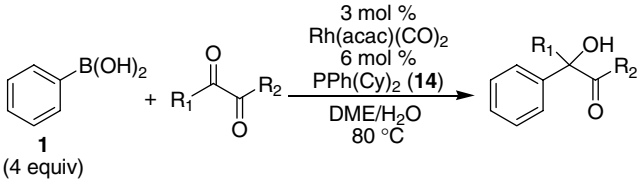
With a promising catalyst-phosphine combination, a number of experimental factors were varied in an effort to further increase the yield of the addition reaction. Phosphine loading studies with dicyclohexylphenyl phosphine **14** showed that a 2:1 ratio of phosphine to rhodium complex was optimal. Further optimization showed that only 3 mol % of the rhodium complex was required for good catalytic activity. Lowering or raising the temperature of the reaction proved detrimental. Allowing the reaction to proceed for more than 24 h also gave no increase in the yield of the transformation. Changing the solvent showed little difference between dioxane, DME, and toluene. Variations in the amount of water (between 1% and 50% water with DME as a cosolvent) also had little effect on the yield.

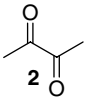
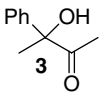
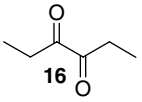
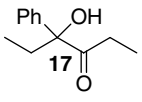
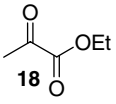
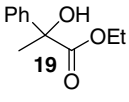
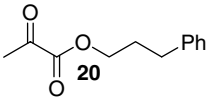
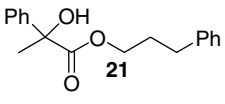
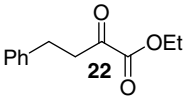
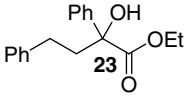
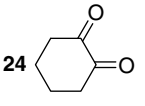
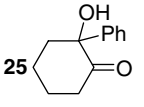
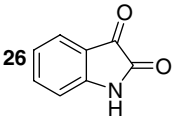
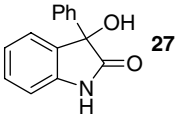
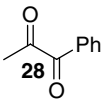
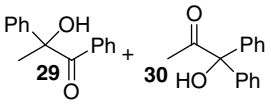
Attempts were also made to improve the reaction through the use of additives. The addition of a base, for example, may activate boronic acids to transmetallation with a metal catalyst.[19] The use of a stoichiometric amount of basic additives (KOH, K_2CO_3, $NaHCO_3$, Et_3N) gave much lower yields of addition products. The use of thallium(I) ethoxide, which has been previously shown to increase the yield of some Suzuki couplings, was also explored to no avail.[22,23] The addition of NMO to facilitate the displacement of the carbon monoxide ligands from the precatalyst also proved detrimental to the overall yield.

Investigation into the ratio of boronic acid to 1,2-diketone proved to be the only fruitful avenue for increasing the reaction yield. The use of excess boronic acid is common in similar systems, especially with electron-poor aryl boronic acids, as protodeborylation can be a competing process.[24] Doubling the amount of boronic acid present in the reaction mixture lead to an 83% yield of the addition product.

With good conditions for the addition of phenylboronic acid to 2,3-butanedione, a number of other electrophiles were used to determine the scope of the addition reaction. Many acyclic 1,2-diketones and 1,2-ketoesters proved to be excellent substrates for addition (Table 2).[25–27] An exception was 1,2-cyclohexanedione (**24**) which gave no addition product. The analysis of 1,2-cyclohexanedione by ^1H NMR showed that the one carbonyl preferred the conjugated enol tautomer, explaining the lack of reactivity as the molecule was more similar to an α,β-unsaturated ketone than a

Table 2. Variation of electrophile

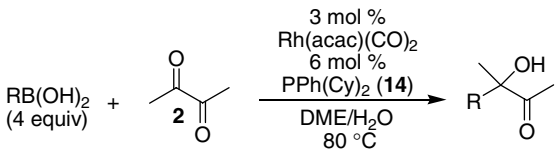


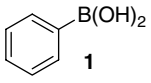
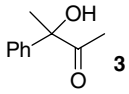
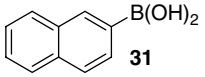
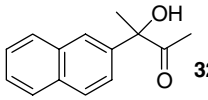
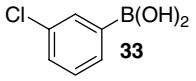
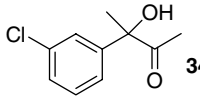
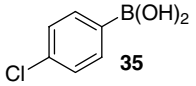
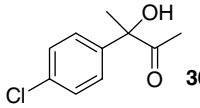
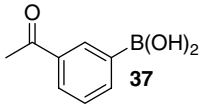
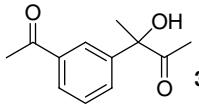
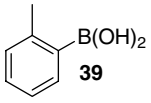
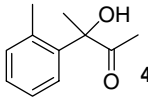
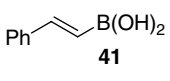
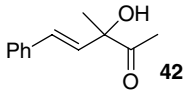
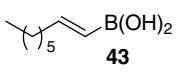
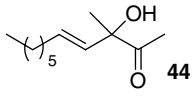
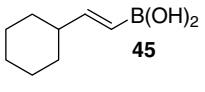
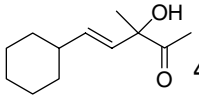
Entry	Electrophile	Product	Yield (%)
1			83
2			54
3			47
4			62
5			64
6			0
7			83
8			42

1,2-diketone. Cyclic substrates that cannot enolize, such as isatin (**26**), gave an excellent yield of the addition products without the need for protection of the amide hydrogen. Unsymmetrical 1,2-diketones provided the mixtures of addition products. For example, 1-phenyl-1,2-propanedione **28** (Table 2, entry 8) provided a 1.7:1 mixture of alcohols **29** and **30**. Sterics or the greater stability imparted by conjugation with the phenyl group can explain the observed product ratio.

The variation of the boronic acid nucleophile was also explored, using 2,3-butanedione as the electrophile (Table 3). The use of boronic acids with electron-withdrawing groups has been shown to be problematic in some systems,[28] but good yields were obtained using electron poor arylboronic acids under these conditions (Table 3, entries 3–5). The use of acetophenone derivative **37** highlighted the excellent functional group tolerance of this method, as the pendant ketone precludes the formation of the corresponding aryllithium or Grignard reagent. The use of the *ortho*-tolylboronic acid provided a lower yield than other cases, which may be due to steric congestion near the reacting centers. Vinylboronic acids were also explored as addition partners (Table 3, entries 7–9). These gave similar yields as the aryl boronic acids.

Table 3. Variation of boronic acid



Entry	Boronic acid	Product	Yield (%)
1	 **1**	 **3**	83
2	 **31**	 **32**	85
3	 **33**	 **34**	67
4	 **35**	 **36**	76
5	 **37**	 **38**	85
6	 **39**	 **40**	31
7	 **41**	 **42**	61
8	 **43**	 **44**	71
9	 **45**	 **46**	74

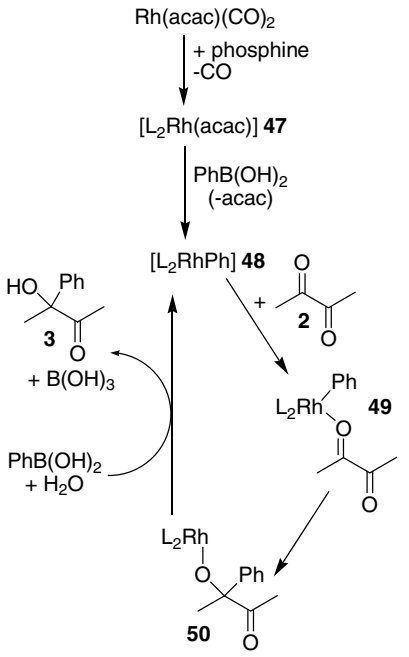


Figure 1. Proposed mechanism of the addition reaction.

A working hypothesis for the mechanism of the addition reaction follows from the studies of Hayashi[29] and Miyura.[11] The active catalyst is generated by the binding of the phosphine to the transition metal (Fig. 1). Under acidic conditions, the β-diketonate ligand is lost and a phenylrhodium intermediate such as **48** is formed. Next, ligand exchange with the reactive carbonyl activates the electrophile for nucleophilic addition. After the addition of the phenyl group to the ketone, the alkoxide is hydrolyzed and the phenylrhodium is reformed by reaction with another equivalent of phenylboronic acid. This results in the formation of the addition product **3** and the turnover of the catalyst.

The rhodium-catalyzed addition of aryl and vinylboronic acids provides a direct route to tertiary α-hydroxy ketones under mild conditions. This cluster of functionality is present in a number of interesting target molecules. The use of rhodium catalysis and boronic acids to affect this addition reaction allows for the formation of a new carbon–carbon bond with excellent functional group tolerance. Further studies on the asymmetric variants of this process will be reported in due course.

Acknowledgment

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References and notes

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25. *Representative experimental procedure*: Ethyl 2-oxo-4-phenyl butyrate **22** (130 mg, 0.611 mmol) was dissolved in 1 mL of 9:1 1,2-dimethoxyethane/H_2O which had been degassed by bubbling argon through it for 20 min. This solution was added to a flask containing dicarbonylacetonato rhodium(I) (5.2 mg, 0.019 mmol, 3 mol %), dicyclohexylphenyl phosphine **14** (10.8 mg, 0.037 mmol, 6 mol %) and phenylboronic acid **1** (317 mg, 2.47 mmol) under argon. The reaction was then heated to 80 °C. After 24 h the reaction was allowed to cool to room temperature, taken up in ethyl ether, washed with 1 N NaOH (3×), dried ($MgSO_4$), and concentrated. Purification by silica gel chromatography (60% CH_2Cl_2/hexanes) provided 111 mg (64%) of alcohol **23** as a thick oil. Compound **23**: TLC $R_f = 0.31$ (60% CH_2Cl_2/hexanes); IR (film from CH_2Cl_2): 3501, 3027, 1726, 1495, 1244, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.67 (m, 2H), 7.16–7.41 (m, 8H), 4.15–4.29 (m, 2H), 3.93 (s, 1H), 2.75 (ddd, 1H, $J = 13.6$, 11.8, 5.2 Hz), 2.62 (dt, 1H, $J = 11.8$, 4.9 Hz), 2.51 (ddd, 1H, $J = 13.4$, 11.6, 5.0 Hz), 2.34 (ddd, 1H, $J = 13.6$, 11.8, 5.0 Hz), 1.27 (t, 1H, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 142.2, 142.1, 128.9, 128.8, 128.7, 128.1, 126.3, 125.9, 78.4, 63.0, 42.0, 30.6. HRMS (ESI): m/z calcd for $C_{18}H_{20}O_3Na$: 307.1304; found, 307.1304.
26. *Characterization data for new compounds* **21**: TLC $R_f = 0.28$ (30% Et_2O/hexanes); IR (neat): 3505, 3061, 2937, 1727, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.63 (m, 10H), 4.22 (dt, 2H, $J = 6.6$, 1.8 Hz), 3.94 (s, 1H), 2.63 (t, 2H, $J = 7.5$ Hz), 2.00 (m, 2H), 1.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 143.3, 141.2, 128.9, 128.8, 128.7, 128.3, 126.6, 125.7, 76.1, 65.9, 32.2, 30.5, 27.0. Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.16; H, 7.08. Compound **38**: TLC $R_f = 0.26$ (CH_2Cl_2); IR (neat): 3453, 3019, 2981, 1714, 1682, 1427, 1358, 1272 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (t, 1H, $J = 1.8$ Hz), 7.91 (ddd, 1H, $J = 7.8$, 1.8, 1.2 Hz), 7.67 (ddd, 1H, $J = 7.8$, 1.8, 1.2 Hz), 7.49 (t, 1H, $J = 7.8$ Hz), 4.61 (s, 1H), 2.58 (s, 3H), 2.11 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 198.2, 142.7, 137.9, 131.2, 129.4, 128.6, 126.0, 80.2, 27.1, 24.7, 23.8. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.28; H, 6.65. Compound **44**: TLC $R_f = 0.29$ (10% ethyl acetate/hexanes); IR (neat): 3470, 2957, 2927, 2856, 1713, 1456 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (td, 1H, $J = 15.3$, 6.9 Hz), 5.51 (td, 1H, $J = 15.3$, 1.5 Hz), 4.01 (s, 1H), 2.22 (s, 3H), 2.02–2.21 (m, 2H), 1.46 (s, 3H), 1.23–1.40 (m, 8H), 0.87 (t, 3H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 133.5, 131.0, 79.1, 32.7, 32.0, 29.3, 29.2, 24.9, 24.0, 23.0, 14.4. HRMS (ESI): m/z calcd for $C_{12}H_{22}O_2Na^+$ ($M+Na^+$): 221.1512; found: 221.1508. Compound **46**: TLC $R_f = 0.27$ (10% ethyl acetate/hexanes); IR (neat): 3481, 2926, 2852, 1712, 1449, 1356 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dd, 1H, $J = 15.6$, 6.6 Hz), 5.46 (dd, 1H, $J = 15.6$, 1.2 Hz), 4.00 (s, 1H), 2.19 (s, 3H), 1.93–2.03 (m, 1H), 1.67–1.75 (m, 1H), 1.44 (s, 3H), 1.01–1.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 138.5, 128.2, 78.7, 40.3, 32.6, 26.0, 25.9, 24.5, 23.5. HRMS (ESI): m/z calcd for $C_{12}H_{20}O_2Na^+$ ($M+Na^+$): 219.1355; found, 219.1351.
27. Compounds **4**,[3] **17**,[30] **19**,[8] **27**,[13] **29**,[8] **30**,[8] **32**,[31] **34**,[2] **36**,[3] **40**,[32] and **42**[33] have been previously reported.
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