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EDGE ARTICLE

Rh(I)-catalyzed enantioselective intramolecular hydroarylation of unactivated ketones with aryl pinacolboronic esters†

Gary M. Gallego and Richmond Sarpong*

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Aryl pinacolboronic esters, which are robust and easily handled boronic acid derivatives, effectively add in an intramolecular 1,2 fashion into unactivated ketone groups in the presence of the rhodium complexes $[Rh(cod)(MeCN)_2]BF_4$ and a tertiary amine base or $[Rh(cod)(OH)]_2$ and bisphosphine ligands. The latter set of conditions has been utilized in the enantioselective synthesis of indanols bearing tertiary alcohol groups. The overall transformation serves as a complement to the use of boronic acids as well as traditional nucleophiles such as Grignards, zinc reagents and lithium reagents for enantioselective, intramolecular additions to unactivated ketones, especially those additions which require nucleophilic partners that need to be handled over multiple steps.

Introduction

Non-aldol C–C bond formations with carbonyl electrophiles, especially *unactivated* ketones (see Fig. 1), traditionally employ organometallic reagents (*e.g.*, M = Li, Mg),[1] which are limited by their relatively high basicity, low functional group tolerance and selectivity, as well as their air and moisture sensitivity. As such, methods that extend the scope of this fundamental transformation in organic synthesis to include nucleophiles that overcome these challenges are highly significant, especially for intramolecular applications. Alternatives to traditional Grignard and organolithium reagents, including organosamarium and organozinc reagents,[2] have been introduced. However, even with these nucleophiles, the C–C bond forming reactions with ketonic groups are plagued by low reactivity and in some cases, radical fragmentation of the resulting 1,2-adduct.[3] In this communication, we report that aryl pinacolboronic esters, which are robust boronic acid derivatives that are easily synthesized, handled and purified, effectively add into unactivated ketone groups in the presence of $[Rh(cod)(MeCN)_2]BF_4$ and a tertiary amine additive or the complex generated from $[Rh(cod)(OH)]_2$ and bisphosphine ligands. Importantly, in the presence of a chiral, non-racemic Josiphos ligand, high enantioselectivities are achieved for the formation of indanol products. This work is especially significant from the standpoint of effecting intramolecular, enantioselective additions using pro-nucleophiles that are easily installed and survive multiple synthetic steps. This variant of intramolecular 1,2-addition is expected to find widespread use in complex molecule synthesis.

During the course of a total synthesis of the natural product G. B. 13, we were faced with the challenge of transforming pyridine bromide **1** (R = Br, Scheme 1) to 1,2-adduct **2**.[4] Surprisingly, a range of traditional tactical manoeuvres (Rieke magnesiation,[5] halogen metal exchange, *e.g.*, with *t*-BuLi, Bu_3SnLi or under Knochel's conditions),[6] and samarium-mediated Barbier conditions, failed to deliver the desired product. Counter to intuition, the difficulty of this transformation was *heightened* by its intramolecular nature, since many of the halogen-metal transformations proved to be incompatible with the ketonic groups. Ultimately, this synthetic impasse was solved by converting bromide **1** (R = Br) to a pinacolboronic ester (R = BPin in **1**), which was converted to **2** by an

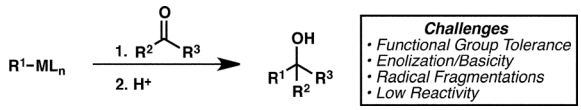
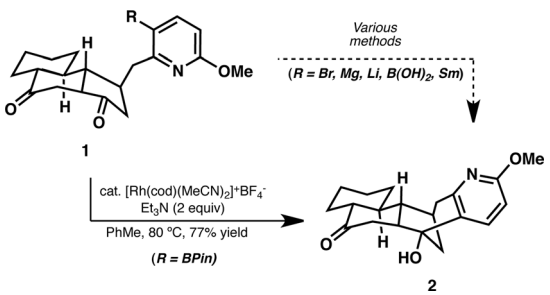


Fig. 1 Additions of organometallics to ketone groups.



Scheme 1 Initial application of Rh(I)-catalyzed 1,2 addition.

University of California, Berkeley, Department of Chemistry, Berkeley, CA, 94720, USA. E-mail: rsarpong@berkeley.edu; Fax: +1 510 642 8369; Tel: +1 510 643 6312

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unprecedented, diastereoselective, 1,2-addition in the presence of catalytic $[Rh(cod)(MeCN)_2]BF_4$ and triethylamine.

Although metal-catalyzed 1,2-additions of aryl organoborons to ketone groups is well precedented, previous reports center almost entirely on the addition of boronic *acids* to *activated* ketones (*e.g.*, cyclobutanones and isatins)[7] or use specialized substrates where nucleophilicity is enhanced. For example, Lu has demonstrated that intramolecular 1,2-addition of aryl boronic acids into ketone groups can be effected with palladium catalysis.[8] However, for the majority of the substrates studied by Lu, an oxygen atom in the linker was necessary as a directing and activating component (see Fig. 2). The addition of aryl boronic *esters*, which are more stable than boronic *acids*, into unactivated ketones is a more attractive option, yet these types of reactions are rare. A lone report by Itami describes a Ni(0)-catalyzed addition of aryl *glycolatoboronic* esters into ketones (Fig. 2).[9] Although this approach provides an elegant solution, the glycolatoboronic esters employed in the study are readily susceptible to decomposition, protodeborylation and hydrolysis.[10] As such, their preparation and utility in complex molecule synthesis, especially in an intramolecular sense where they are carried through multiple synthetic steps, has rather bleak prospects. The only other reported example of aryl organoboron addition into an unactivated ketone is also intermolecular and utilizes sodium tetraphenylboronate.[11] The requirement for tetraarylboronates is inherently limiting in scope, especially for intramolecular applications.

To our knowledge, prior to our 2009 disclosure, there were no reports describing the addition of aryl pinacolboronic esters into unactivated ketones.[12] These latent nucleophiles offer many advantages including air and moisture tolerance, which makes them easy to handle and purify in a laboratory setting. Furthermore, pinacolboronic esters can be carried through multiple synthetic manipulations, which makes these functional groups ideal for complex molecule synthesis, where intramolecular applications are more common. Finally, the installation of the pinacolboronic ester group is readily accomplished using mild methods including the Miyaura coupling,[13] as well as site-selective Ir(I)- and Rh(I)-catalyzed C–H functionalization.[14]

Although a Rh(I)-catalyzed addition of an aryl pinacolboronic ester into a ketone group had been successful for our specific substrate in our synthesis of G.B. 13 (see **1** to **2**, Scheme 1), the reaction conditions proved to be capricious at best for a range of other substrates (*e.g.*, **6a**, Table 1, was obtained in only 32% yield). The outcomes ranged from incomplete reaction over extended reaction times to low yields of the 1,2-adduct. As such, our initial studies to develop a reaction of wide scope focused on identifying reaction conditions for 1,2-addition that were general. These endeavors established the necessity of a tertiary amine base additive, with DABCO emerging as the most effective. Using $[Rh(cod)(MeCN)_2]BF_4$ as the catalyst, a survey of different reaction temperatures and solvents established a temperature range of 80–100 °C and benzene to be optimal for the majority of substrates.

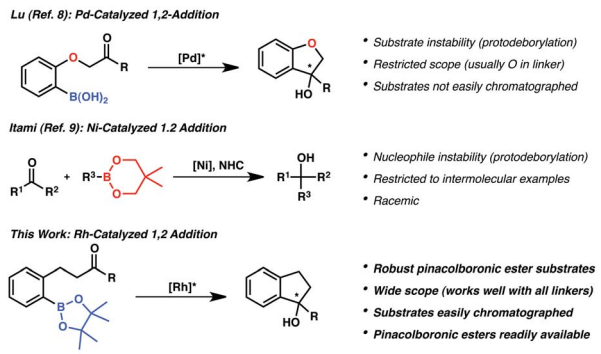


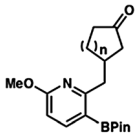
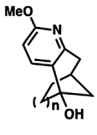
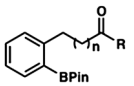
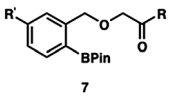
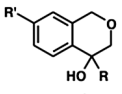
Fig. 2 Examples of metal-catalyzed hydroarylation of unactivated ketones with organoboron nucleophiles.

As shown in Table 1, a range of substrates undergo 1,2-addition including methoxypyridine pinacolboronic esters (entry 1). These heteroaryl boronic esters are converted to bicyclic tertiary alcohols in excellent yields. Less activated aryl pinacolboronic esters (entry 2) also provide the desired tertiary alcohols in good yields with aryl ketones (entry 2c) being the exception. Notably, sterically encumbered ketone substrates readily participate in the cyclization (entries 2f and 3c). As shown in entry 3, substrates bearing an oxygen heteroatom in the tether are well tolerated and provide good yields of the cyclization product, even in the presence of a strongly deactivating group on the arene (entry 3c).

A catalytic cycle for the Rh(I)-catalyzed 1,2-addition, consistent with well established precedent from Hayashi and others,[15] is shown in Scheme 2. The initial step is likely an amine base assisted transmetallation from boron to rhodium to deliver **B**. The amine may coordinate the boron center to create a more active boronate complex that facilitates transmetallation.[16] This assertion is supported by our observation that reaction efficiency increases as we move from less nucleophilic amines (*e.g.*, DBU) to more nucleophilic amines such as DABCO.[17] Following coordination of the ketone carbonyl group to the Rh center, migratory insertion delivers rhodium alkoxide **D**. A key transmetallation of **D** with another molecule of the starting material regenerates **B**. This final transmetallation may be enhanced by the highly nucleophilic character of DABCO, which may (1) form a boronate with another aryl pinacolboronic ester or (2) displace the alkoxide ligand from the metal center to generate an even more electrophilic, cationic, Rh complex.[18] A similar amine base-assisted transmetallation has been proposed by Corey for 1,4-additions of organoboron reagents.[19]

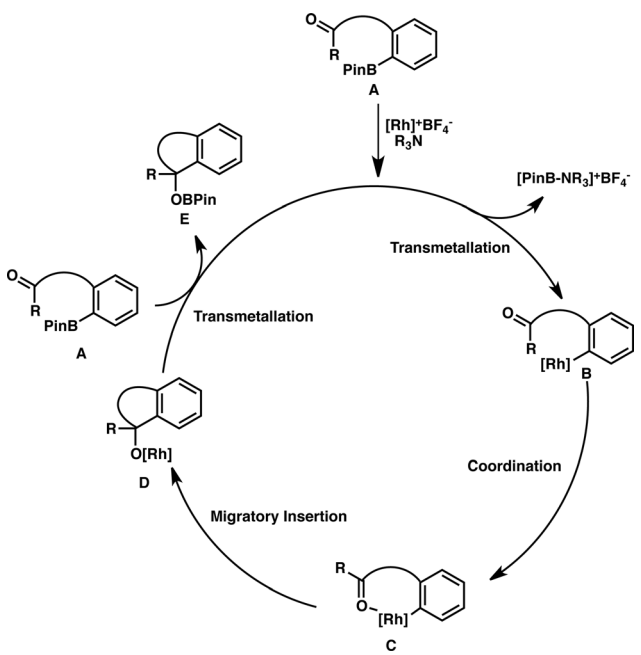
The low conversion and isolated yields associated with the reaction of aryl ketones (see entry 2c, Table 1) prompted us to undertake an optimization study focused on these substrates (Table 2). We hypothesized that the transmetallation step could be facilitated by a hydroxide ligand,[20] and observed a slight improvement in conversion when $[Rh(cod)(MeCN)_2]BF_4$ was replaced with $[Rh(cod)(OH)]_2$ as the catalyst (compare entries 1 and 2, Table 2). Anticipating that a more electron-rich metal center would more easily promote the 1,2-addition to the carbonyl group (*i.e.*, facilitate the migratory insertion step, see Scheme 2), we decided to investigate a range of phosphine ligand additives. Bisphosphine ligands quickly proved to be superior and the bite angle of the bidentate phosphine ligands significantly affected reaction efficiency. In contrast to metal-catalyzed organoboron addition to activated ketones and aldehydes,[21] phosphine ligand additives with larger bite angles (dppf, dppb), as well as BINAP, led to poorer conversions (entries 4–6),

Table 1 Substrate scope of intramolecular 1,2-addition reactions

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1[b]	 3	 4		
	a) n = 1		24	96
	b) n = 2		24	90
	c) n = 3		24	87
2[c]	 5	 6		
	a) n = 1, R = nPr		20	81
	b) n = 1, R = nBu		20	58
	c) n = 1, R = *p*-F(C_6H_4)		58	23[d]
	d) n = 2, R = Me		24	78
	e) n = 2, R = *i*Bu		24	83
	f) n = 2, R = *i*Pr		24	94
3[c]	 7	 8		
	a) R = *i*Bu, R′ = H		24	62
	b) R = *i*Pr, R′ = H		24	67
	c) R = *i*Pr, R′ = F		24	80

[a] Isolated yields. [b] Reaction conditions: 2 equivalents of DABCO, 10 mol% $[Rh(cod)(MeCN)_2]BF_4$, 0.10 M in PhMe, 100 °C. [c] Reaction conditions: 2 equivalents of DABCO, 10 mol% $[Rh(cod)(MeCN)_2]BF_4$, 0.10 M in PhH, 80 °C. [d] 15 mol% catalyst loading.

whereas dppe, which has a smaller bite angle, facilitates smooth conversion to the desired addition product (entry 7). Of note, moving to dppm proved to be detrimental. Using the optimized conditions (5 mol% $[Rh(cod)(OH)]_2$, 10 mol% dppe, PhH, 80 °C), aryl ketones **9–11** (Scheme 3) are now converted to the 1,2-adducts in good isolated yield.[22]

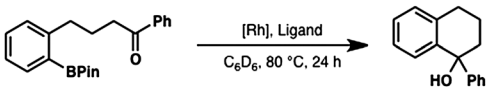


Scheme 2 Proposed catalytic cycle of Rh(I)-catalyzed 1,2-addition.

Finally, the discovery of the $[Rh(cod)(OH)]_2$/dppe conditions for 1,2-adduct formation between pinacolboronic esters and ketone groups (Table 2, entry 7) bolstered prospects for enantioselective variants using chiral bisphosphine ligand additives.[23] Chiraphos (Fig. 3) was selected for our initial enantioselectivity studies (Table 3, entry 1) on the basis of its similarity to dppe which was successful in our optimization studies. Unfortunately, only minimal enantioselectivity (11% ee) was observed. We next investigated BINAP as a ligand because of its documented success in Rh-catalyzed conjugate addition reactions of organoboron compounds.[24] A modest enhancement in ee to 49% was observed in the best case (entry 2). Following an extensive screen of various other ligands, we finally investigated a series of Josiphos ligands[25] and observed a marked increase in enantioselectivity to 85% ee (entry 3) using **L1** (Fig. 3), although this reaction did not proceed to completion. A change in solvent from benzene to toluene led to improved conversion and enantioselectivity (entry 4) and finally, increasing the reaction temperature to 85 °C led to complete conversion and importantly, retained the high enantioselectivity (entry 5).

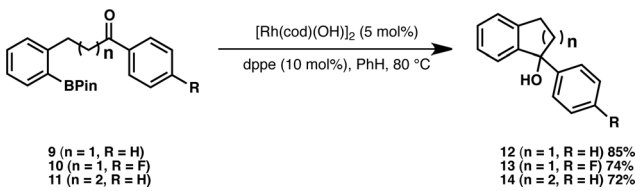
Using these optimized conditions, we have explored the scope of the Rh-catalyzed enantioselective hydroarylation reaction (Table 4). A wide range of aryl ketone substrates, including electron-neutral (entry 1), electron-rich (entry 2), relatively

Table 2 Optimization of 1,2-addition of aryl pinacolboronic esters into aryl ketones



Entry	Catalyst (mol%)	Ligand	Product : SM[a]
1	$[Rh(cod)(MeCN)_2]BF_4$(10)	DABCO(2 equiv)	2.0 : 1.0
2	$[Rh(cod)(OH)]_2$(5)	DABCO(2 equiv)	3.7 : 1.0
3	$[Rh(cod)(OH)]_2$(5)	—	2.6 : 1.0
4	$[Rh(cod)(OH)]_2$(5)	dppf(0.1 equiv)	0.9 : 1.0
5	$[Rh(cod)(OH)]_2$(5)	dppb(0.1 equiv)	0.7 : 1.0
6	$[Rh(cod)(OH)]_2$(5)	BINAP(0.1 equiv)	7.9 : 1.0
7	$[Rh(cod)(OH)]_2$(5)	dppe(0.1 equiv)	>20 : 1
8	$[Rh(cod)(OH)]_2$(5)	dppm(0.1 equiv)	0.2 : 1.0

[a] Ratios determined by ^{1}H NMR.



Scheme 3 1,2-Addition into aryl ketones.

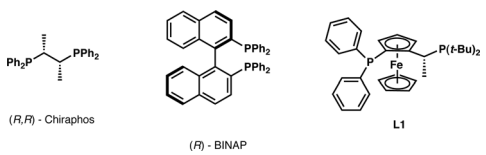
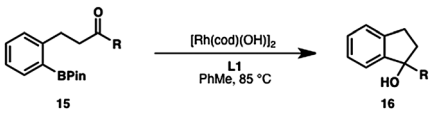


Fig. 3 Selected bisphosphine ligands.

sterically encumbered (entry 4) and electron-poor (entry 5) variants uniformly give indanol products with good to high enantioselectivity.[26] An alkyl ketone has also been shown to undergo hydroarylation with good levels of enantiocontrol under the optimized conditions (entry 6).

Table 4 Enantioselective hydroarylation reactions[a]



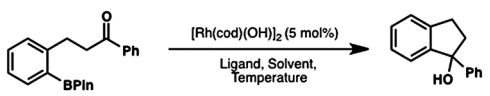
Entry	R	Yield (%)[b]	% ee[c]
1	a) Ph	78	94
2	b) *m*-MeO(C_6H_4)	85	95
3	c) *p*-Tol	90	94
4	d) 2-Nap	50	93
5	e) *p*-F(C_6H_4)	54	92
6	f) Me	90	95

[a] Reaction conditions: 5 mol% $[Rh(cod)(OH)]_2$, 11 mol% **L1**, 0.1 M in PhMe. [b] Isolated yields. [c] Determined by chiral HPLC.

Conclusions

In conclusion, we report the first examples of addition of aryl pinacolboronic esters into unactivated ketones, which are catalyzed by Rh(I) complexes. Historically, aryl pinacolboronic ester pro-nucleophiles have been viewed as relatively inert in addition reactions to ketone groups. These intramolecular Rh(I)-catalyzed

Table 3 Optimization of enantioselective ketone hydroarylation



Entry	Ligand (mol%)	Solvent	Temp (°C)	Time (h)	Product : SM[a]	% ee[b]
1	(*R*,*R*)-Chiraphos(10)	C_6D_6	80	48	1.0 : 0	11(74)[c]
2	(*R*)-BINAP(10)	C_6D_6	80	24	1.0 : 0	49
3	**L1**(11)	C_6D_6	80	72	1.5 : 1.0	85
4	**L1**(11)	PhMe	80	72	5.7 : 1.0	94(69)[c]
5	***L1****(11)*	*PhMe*	*85*	*72*	*1.0 : 0*	*94*(78)[c]

[a] Ratios determined by ^{1}H NMR. [b] Enantiomeric excess determined by chiral HPLC. [c] Values in parentheses are isolated yields.

hydroarylation reactions are efficient and high yielding. This work demonstrates the feasibility of the readily prepared and easily handled pinacolboronic ester group as a latent nucleophilic handle in 1,2-addition reactions. This reactivity complements established aryl addition reactions that use boronic acids or glycolatoboronic esters. Furthermore, the enantioselective hydroarylation of aryl and alkyl ketones proceed with very good levels of enantiocontrol.

Acknowledgements

Kimberly K. Larson is acknowledged for the initial discovery of this transformation in the context of the synthesis of G. B. 13. The work was supported by a grant from the NIH-NIGMS (RO1 086374). We are thankful to Amgen, Eli Lilly and Roche for financial support. We also thank Solvias (Benoit Legault) for the kind donation of ligands.

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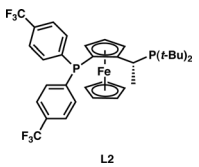
21 See ref. 7*b*, *c* and 11 as well as: (*a*) M. Sakai, M. Ueda and N. Miyaura, *Angew. Chem., Int. Ed.*, 1998, **37**, 3279; (*b*) M. Ueda and N. Miyaura, *J. Org. Chem.*, 2000, **65**, 4450.
22 The application of the conditions optimized for aryl ketones (5 mol% $[Rh(cod)(OH)]_2$, 10 mol% dppe, 0.1 M in PhH, 80 °C, 24 h) to the alkanone substrate **5f** leads to a 92% yield of **6f**, which is comparable to the yield obtained using the original conditions (2 equivalents of DABCO, 10 mol% $[Rh(cod)(MeCN)_2]BF_4$, 0.1 M in PhH, 80 °C, 24 h).
23 For a comprehensive list of optimization studies, see the Supporting Information†.
24 T. Hayashi, *Pure Appl. Chem.*, 2004, **76**, 465.
25 Of note, Cramer has demonstrated previously that aryl-rhodium intermediates (accessed *via* β-carbon scission) can add into ketones with high ee using **L2**:



L2

T. Seiser, O. A. Roth and N. Cramer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6320.
26 Extending the optimized conditions to the formation of larger rings (*e.g.*, tetralinols) proceeds with low enantioselectivity. For example, **5f** undergoes cyclization to yield **6f** in 86% yield, but in a moderate 46% ee.

