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New Synthesis of Furans: the Rhodium-Catalysed Carbonylative Addition of Arylboronic Acids to Propargylic Alcohols/ Cyclisation Sequence

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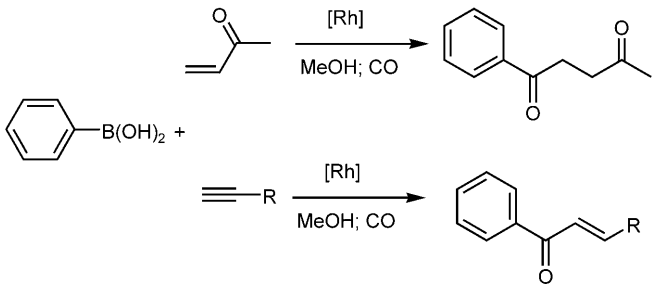
Abstract: The rhodium-catalysed carbonylative addition of arylboronic acids to propargylic alcohols yields gamma-hydroxy enones that are readily cyclised through a dehydration step to the corresponding furan analogues. The transformation was improved thanks to the screening of the reaction conditions and consequent improvements were obtained from the use of dicarbonylrhodium iodide $[Rh(CO)_2I]_2$ as catalyst precursor. The generalisation of the reaction was then further investigated by employing variously substituted arylboronic acids and propargylic alcohols.

Keywords: boron; carbonylation; C–C bond formation; furans; rhodium

Introduction

The hydroacylation reaction of alkynes allows a fast access to α,β-unsaturated ketones, important building blocks in organic synthesis.[1] Various acylating reagents have been introduced for this purpose. Stoichiometric organometallic, unmasked acylation reagents were extensively developed and reacted with alkynes.[2] However, this strategy is limited by the large wastage of metal needed for the synthesis of the targeted ketones. Thus, it turns out that alternative reactions that would involve catalytic amounts of metal are needed for economic and environmental reasons. The catalytic activation of the C–H bond of aldehydes to generate the nucleophilic acyl equivalent is an elegant and straightforward methodology to perform clean hydroacylation reactions.[3] In addition to an often hard activation of the C–H bond of the aldehyde with mainly rhodium salts, the thus formed metal-acyl intermediate is often susceptible to decarbonylation, particularly at the high temperatures required to perform the former C–H activation step. This limitation has been partially overcomed by using aldehydes that bear chelating functionalities. Another approach is the generation of the targeted metal-acyl reagent through a carbonylation step, that is, the insertion of a carbon monoxide molecule in a metal-carbon bond. Although carbon monoxide has been widely used to prepare various stoichiometric organometallic acylation reagents, catalytic carbonylative hydroacylation reactions of unsaturated compounds are rather uncommon. The earlier examples deal with C–H activation of benzene with rhodium precursors,[4] pyridines[5] and imidazoles[6] with ruthenium clusters. Under CO pressure, the thus obtained metal acyl derivatives are reacted with olefins for ketone synthesis. Later, transmetallation of the organic moiety of an organozinc reactant from zinc to a palladium centre followed by a carbonylation step also allowed the generation of an acylation reagent which could be reacted with α,β-unsaturated ketones.[7] In our laboratory, we used the transmetallation of the aryl group from the boron of an organoboron reagent to a rhodium centre to form the metal-carbon bond. Under CO, such an intermediate is carbonylated and affords rhodium-aroyl intermediates that could be reacted with vinyl ketones to synthesise 1,4-diketones (Scheme 1).[8] The



Scheme 1. Rhodium-catalysed addition of arylboronic acids to vinyl ketones and alkynes.

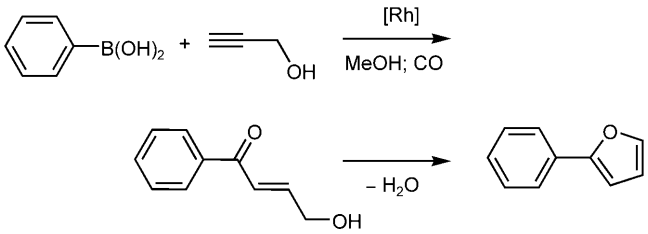
scope of this concept was further enlarged to the azabicycle opening reaction[9] and hydroacylation of internal and terminal alkynes.[10]

We now report the reaction with functionalised alkynes such as propargyl alcohols. The product of the reaction is not the originally expected γ-hydroxy enone but a furan obtained through the rhodium-catalysed hydroacylation reaction followed by a cyclisation step.

Results and Discussion

In a first set of experiments, we investigated the reaction between one equivalent of phenylboronic acid and one equivalent of propargyl alcohol (Scheme 2) using the optimised reaction conditions previously reported with 1-heptyne.[10b] After one night of reaction, GC-MS analysis of the crude did not show the formation of the expected γ-hydroxy enone but evidenced the formation of 2-phenylfuran. The structure of 2-phenylfuran was confirmed by ^{1}H and ^{13}C NMR spectroscopy of the product isolated by silica gel column chromatography.

In addition, the GC analysis proved the formation of benzene, likely obtained from the proto-deboronation reaction of the phenylboronic acid.[11] Although the γ-hydroxy enone was not observed in the run, its formation as intermediate was very likely as γ-hydroxy enones are known to readily dehydrate into furans under acidic conditions.[12]



Scheme 2. Rhodium-catalysed carbonylative addition of phenylboronic acid to propargyl alcohol.

This is clearly evidenced upon analysing the reaction during a catalytic run (Figure 1). The first minutes of the reaction show the formation of the expected γ-hydroxy enone rapidly followed by the formation of the 2-phenylfuran. After 3 h, the rate of cyclisation becomes higher than the rate of hydroacylation and, consequently, the amount of γ-hydroxy enone drops until its complete disappearance which fits with the maximum amount of 2-phenylfuran obtained. The cyclisation reaction is known to be acid-catalysed and it is likely that the combination of the reaction temperature with the presence of phenylboronic acid is enough to promote the cyclisation. The formation of benzene is observed at the end of the reaction when most of the propagyl alcohol has been consumed.

A fast screening of the reaction conditions was made in order to further improve the yield in 2-phenylfuran (Table 1). The nature of the solvent is a critical parameter and it is noteworthy that the reaction does only afford the product in alcoholic solvents (compare entries 1–3 with 4 and 5). As it has been precedently observed with the parent reactions involving methyl vinyl ketone or alkynes, methanol proved to be the solvent of choice for this reaction. Temperatures of 80 or 90 °C are suitable to ensure a complete conversion of the alkyne, the latter giving the best yield (entries 5 and 7). At 60 °C, the conversion of the propargyl alcohol is not complete and at 100 °C the amount of benzene formed becomes strongly limiting (entries 6 and 8). Concerning the influence of the CO pressure, it is noteworthy that an optimum was reached with 5 bar CO. At higher CO

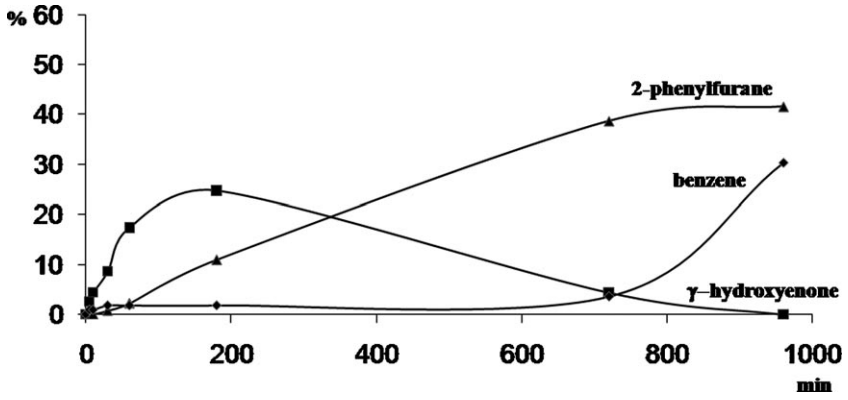


Figure 1. Rhodium-catalysed carbonylative addition of phenylboronic acid to propargy alcohol. The reactions were run with propargyl alcohol (2.3 mmol), $PhB(OH)_2$ (1.5 mmol); $[Rh(COD)Cl]_2$ (0.0075 mmol; 1% Rh) in 30 mL MeOH at 80 °C with 5 bar CO for 18 h. Y axis: % yields in 2-phenylfuran, benzene and γ-hydroxy enone calculated from the amount of phenylboronic acid used; X axis: reaction time in minutes.

Table 1. Influence of the reaction parameters on the yield in phenylfuran.[a]

Entry	Solvent	T [°C]	P_{CO} [bar]	Conversion [%]	Yield [%]
1	CH_3CN	80	5	52	0
2	THF	80	5	73	0
3	DMF	80	5	47	0
4	1-propanol	80	5	70	11
5	MeOH	80	5	>95	32
6	MeOH	60	5	14	0
7	MeOH	90	5	>95	42
8	MeOH	100	5	>95	25[b]
9	MeOH	80	20	89	25[c]
10	MeOH	80	10	85	24
11	MeOH	80	2	>95	13
12	MeOH	80	1	89	19

[a] The reactions were run with propargyl alcohol (2.3 mmol), $PhB(OH)_2$ (1.5 mmol); $[Rh(CO)_2Cl]_2$ (0.0075 mmol; 1% Rh) in 10 mL solvent for 18 h. The yields and conversions were determined by GC using undecane as internal standard.

[b] 44% of benzene was formed.

[c] 13% of benzene and 3% of benzophenone were also formed.

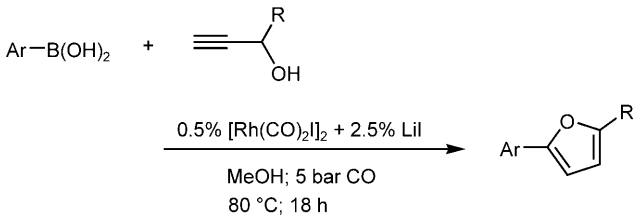
pressure, typically 20 bar, not negligible amounts of benzene and benzophenone were formed. Benzophenone is formally obtained from the carbonylative coupling reaction of two phenylboronic acids. A CO pressure of 5 bar was further used for the overall study.

A screening was made using several rhodium precursors (Table 2). The combination of a phosphorus-based ligand with $[Rh(COD)Cl]_2$ is strongly limiting and in all cases led to lower yields (entries 1–5). The amount of 2-phenylfuran obtained was decreased with increasing phosphorus content in the reaction medium. If a reasonable yield was attained using one equivalent of PPh_3, the use of a diphosphine or $RhCl(CO)(PPh_3)_3$ led to disappointing results. The nature of the X-type ligand is also drastically important. The presence of a hydroxide or methoxide group in place of the chloride gives completely unreactive complexes (entries 1, 8 and 9). The same conclusion is made with a cationic rhodium precursor. It turned out that the halogen has an important role in the course of the reaction. We thus focused our attention to an alternative to the chloride by using $[Rh(CO)_2I]_2$. This complex indeed led to significant improvements in the yield (Scheme 3). A further improvement was reached after the use of an additional amount of lithium iodide in combination with this precursor. The combination of lithium iodide with the commercially available complex $[Rh(CO)_2Cl]_2$ does not give the same improvement of yield. Although this effect cannot be easily rationalised, it is noteworthy that the use of an iodide ligand has led to important improvements in several catalytic reactions.[13] Although no oxidation reaction is involved in our case, we believe that the action of iodide as ligand *versus* rhodium is the source of the improved selectivity. Yields and conversions were determined by GC using undecane as internal standard.

Table 2. Influence of the nature of the catalytic precursor on the yield in phenylfuran.[a]

Entry	Rh precursor	Additive	Conversion [%]	Yield [%]
1	$[Rh(COD)Cl]_2$	–	>95	41
2	$[Rh(COD)Cl]_2$	1% PPh_3	>95	17
3	$[Rh(COD)Cl]_2$	1% $P(OPh)_3$	>95	23
4	$[Rh(COD)Cl]_2$	1% dppe	>95	7
5	$RhCl(CO)(PPh_3)_3$	–	35	0
6	$[Rh(CO)_2Cl]_2$	–	>95	37
7	$[Rh(NBD)Cl]_2$	–	>95	18
8	$[Rh(COD)OMe]_2$	–	45	0
9	$[Rh(COD)OH]_2$	–	68	0
10	$[Rh(COD)_2^+]BF_4^-$	–	17	0
11	$[Rh(CO)_2I]_2$	–	>95	45
12	$[Rh(CO)_2I]_2$	2.5% LiI	>95	66
13	$[Rh(CO)_2I]_2$	5% LiI	>95	58
14	$[Rh(CO)_2Cl]_2$	2.5% LiI	>95	35

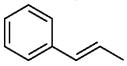
[a] The reactions were run with propargyl alcohol (2.3 mmol), $PhB(OH)_2$ (1.5 mmol); a rhodium precursor (0.0075 mmol; 1% Rh) in 10 mL MeOH at 80 °C with 5 bar CO for 18 h.



Scheme 3. Rhodium-catalysed carbonylative addition of arylboronic acid to propargyl alcohol.

Various propargyl alcohols and arylboronic acids were used in order to study the scope of the reaction (Table 3). The products were purified by silica gel column chromatography and identified by ^1H and ^{13}C NMR spectroscopy. The yield of 2-arylfurans obtained from the reaction between propargyl alcohol and an arylboronic acid is strongly dependent on the nature of the substituents on the aryl moiety. *para*-Electron-donating substituent groups like a methyl or methoxy allow similar yields as those obtained from the phenylboronic acid (entries 2 and 3). In these two cases, the GC analysis of the crude showed the presence of non cyclised γ-hydroxy enone that can be completely converted into furan by refluxing the mixture with one drop of concentrated hydrochloric acid. The presence of the methyl substituent on an *ortho*-

Table 3. Synthesis of furans.[a]

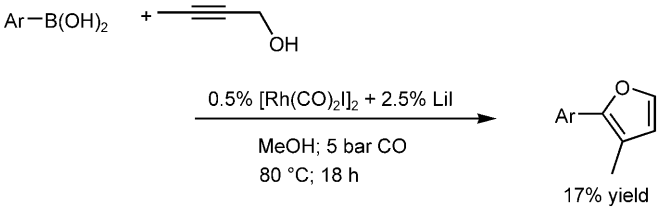
Entry	Ar	R	Yield [%][b]
1	Ph	H	60
2	*p*-MeC_6H_4	H	65
3	*p*-$MeOC_6H_4$	H	45
4	*o*-MeC_6H_4	H	6
5	*p*-FC_6H_4	H	57
6	*p*-ClC_6H_4	H	35
7	*m*-ClC_6H_4	H	10
8		H	41
9	Ph	Me	78
10	Ph	Ph	64
11	Ph	*p*-ClC_6H_4	42

[a] The reactions were run with propargyl alcohol (2.3 mmol), $ArB(OH)_2$ (1.5 mmol); $[Rh(CO)_2I]_2$ (0.0075 mmol) and LiI (0.037 mmol) in 10 mL MeOH at 90 °C with 5 bar CO for 18 h.

[b] Isolated yields.

position of the phenyl ring greatly impedes the reaction for probably steric reasons (entry 4). *para*-Substituted phenyl groups with a fluoride or chloride can also be converted into furans (entries 5 and 6). However, the *meta*-position of the chloride leads to very low yield in expected product (entry 7). Styrylboronic acid can be used for the synthesis of 2-styrylfurans (entry 8), broadening the scope of the reaction to the use of vinylic boronic acids. Propargyl alcohols substituted with an alkyl or aryl group on the propargylic carbon can also be converted into 2,5-disubstituted furans as well (entries 9 and 10).

Finally, internal alkynes could be reacted but lead to low yields in furan. The reaction between phenylboronic acid and but-2-yn-1-ol yielded the 2-phenyl-3-methylfuran with only 17% yield (Scheme 4).



Scheme 4. Rhodium-catalysed carbonylative addition of phenylboronic acid to but-2-yn-1-ol.

Conclusions

In conclusion, we have developed a new synthetic pathway to access 2- and 2,5-substituted furans from propargyl alcohol, aryl- or vinylboronic acid, carbon monoxide and a proton source. This new catalytic reaction is best promoted by iodide-containing rhodium complexes. The catalytic sequence involves a carbonylative hydroacylation of the triple bond to yield a γ-hydroxy enone which is *in situ* converted in furan through a dehydration step.

Experimental Section

General Remarks

All reactions were performed under a dry carbon monoxide and nitrogen atmosphere. Methanol was distilled from Mg and stored under nitrogen prior to use. Propargyl alcohol, 1-phenyl-2-propyn-1-ol, but-2-yn-1-ol and arylboronic acids were purchased from Sigma–Aldrich. 1-(*p*-Chlorophenyl)-2-propyn-1-ol was synthesised according to a reported procedure by reaction between sodium acetylide and benzaldehyde.[14] Propargyl alcohol was distilled from CaH_2 prior to use, the other propargylic alcohols were used without further purification. $[Rh(CO)_2I]_2$ was synthesised according to a reported method.[15] Flash chromatography for product purification was performed using silica gel (Macherey–Nagel, 60 Å, 230–400 mesh). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker AV300 spectrometer at 300 MHz. Chemical shifts were determined relative to internal standard peaks and deuterated solvents (TMS at $\delta = 0$ ppm for protons, $CDCl_3$ at $\delta = 77.23$ ppm for carbon atoms). GC analyses for yield determinations were performed on a Varian 3900 chromatograph. MS analysis were performed on a Polaris Q from Thermoelectron (San Jose, USA).The instrument was calibrated using FC43 (perfluorotributylamine) reference. The chemical ionisation (CI) reagent gas was methane with a 2 mL min^{-1} flow rate. Mass spectra were acquired over the range *m*/*z* 40 to 450 in positive ionisation mode. The source temperature is 200 °C. 2-Phenylfuran, 2-(*p*-tolyl)furan,[16] 2-(*p*-methoxyphenyl)furan,[17] 2-(*o*-tolyl)furan,[17] 2-(*p*-chlorophenyl)furan,[16] 2-(*m*-chlorophenyl)furan,[18] 2-styrylfuran,[18] 2-phenyl-5-methylfuran,[8b] 2,5-diphenylfuran[19] and 2-phenyl-5-(*p*-chlorophenyl)furan as well as 2-phenyl-3-methylfuran[20] are known products, the ^1H and ^{13}C NMR spectra obtained for these compounds were in accordance with the reported data.

General Procedure for the Carbonylative Addition of Arylboronic Acids to Propargylic Alcohols

Arylboronic acid (1.5 mmol), $[Rh(CO)_2I]_2$ (0.0075 mmol) and LiI (0.037 mmol) were introduced in a 100-mL stainless steel autoclave and purged three times with nitrogen. In a Schlenk tube flushed with nitrogen, the propargylic alcohol (2.3 mmol) and the internal standard (142 μL) were dissolved in methanol (10 mL). The solution was transferred with a syringe into the autoclave, which was then pressurised with 5 bar of carbon monoxide and heated at 80 °C with an oil bath. After 18 h, the autoclave was cooled to room temperature and depressurised. The pure products were isolated by flash chromatography (*n*-hexane/diethyl ether: 95/5).

2-(*p*-Fluorophenyl)furan: Orange oil; ^1H NMR ($CDCl_3$): $\delta = 7.63$ (dd, $^3J_{H,F} = 5.3$ Hz, $^3J_{H,H} = 8.8$ Hz, 2H), 7.45 (d, $^3J_{H,H} = 1.3$ Hz, 1H), 7.07 (d, $^3J_{H,H} = 8.8$ Hz, 2H), 6.58 (d, $^3J_{H,H} = 3.2$ Hz, 1H), 6.45 (dd, $^3J_{H,H} = 1.8$ and 3.2 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 162$ (d, $J_{C,F} = 245$ Hz), 153.2, 142,

127.3, 125.5 (d, $J_{C,F}=7.5$ Hz), 115.6 (d, $J_{C,F}=21.8$ Hz), 111.7, 104.6; MS (EI): $m/z=162$ (M^+).

2-Phenyl-5-(*p*-chlorophenyl)furan: Yellow solid; ^{1}H NMR ($CDCl_3$): $\delta=7.73$ (d, $^3J_{H,H}=7.4$ Hz, 2H), 7,66 (d, $^3J_{H,H}=8.6$ Hz, 2H), 7.43–7.35 (m, 4H,), 7.28 (t, $^3J_{H,H}=7.5$ Hz, 2H), 6.73 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=153.9$, 152.5, 133.1, 130.7, 129.5, 129.1, 129, 127.8, 125.1, 124, 107.9, 107.5; MS (EI): $m/z=154$ (M^+).

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