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Baylis–Hillman adducts in rhodium-catalyzed 1,4-additions: unusual reactivity†

Laure Navarre, Sylvain Darses* and Jean-Pierre Genet*

Laboratoire de Synthèse Sélective Organique (UMR 7573, CNRS), Ecole Nationale Supérieure de Chimie de Paris, 11 rue P&M Curie, 75231 Paris cedex 05, France. E-mail: darses@ext.jussieu.fr; genet@ext.jussieu.fr; Fax: +33 1 44 07 10 62; Tel: +33 1 44 27 67 43

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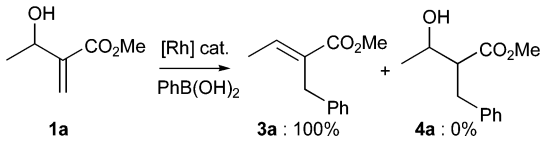
In the presence of a rhodium catalyst, unactivated Baylis–Hillman adducts reacted with arylboronic acids to afford trisubstituted alkenes with good yields. This highly efficient reaction (aerobic conditions, low temperature) is believed to proceeds *via* an unexpected mechanism involving 1,4-addition/β-hydroxy elimination steps and not π-allyl type rhodium intermediates.

The Baylis–Hillman (BH) reaction is a powerful carbon–carbon bond forming reaction between electrophiles and activated vinylic systems.[1] The products of this reaction, the Baylis–Hillman adducts, containing a minimum of three chemospecific functional groups, *i.e.* hydroxy, alkene and electron-withdrawing groups, offer huge opportunities for further transformations. Despite the important development of methodologies to functionalize these substrates, their use in transition metal catalyzed C–C bond formation reactions is scarce.[1] However, bearing both allyl alcohol and activated alkenes moieties, these substrates present attractive features in π-allyl chemistry[2] or in Michael type additions.[3] Indeed thanks to their α,β-unsaturated ester moiety, the BH substrates have been used successfully in palladium-catalyzed Heck reactions.[1c] But, most of the time, Baylis–Hillman adducts have been functionalized *via* S_N2'[4] or π-allyl type mechanisms.[5,6] These reactions generally required the activation of the hydroxyl with the intermediate formation of acetate or carbonate. For example, Kabalka *et al*.[6] have reported that potassium trifluoro(organo)borates[7] participated in palladium-catalyzed cross-coupling with acetates of BH adducts allowing the formation of stereodefined alkenes[8] *via* π-allylpalladium intermediates.

The use of non activated Baylis–Hillman adducts would be more desirable, particularly from the viewpoint of atom economy,[9] but these substrates, as well as more generally allylic alcohols,[10] have proven to be usually reluctant to participate in transition metal catalyzed reactions. Being engaged for some years in 1,4-additions of organoboron reagents to Michael acceptors catalyzed by rhodium(I),[11] we were interested in testing the reactivity of non activated BH adducts in such reactions. Whereas it has been shown in some papers that boron reagents could be used as nucleophiles in coupling reaction with allyl acetates,[12] non-activated allylic alcohols are generally inactive, except in ionic liquid medium.[13] In this paper, we wish to report that organoboronic acids add very efficiently to non activated Baylis–Hillman adducts in the presence of rhodium catalyst thanks to an *unusual reactivity*.

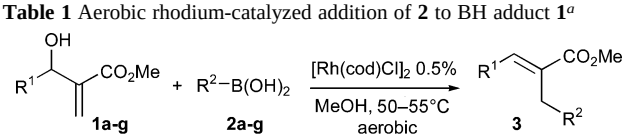


1a **3a** : 100% **4a** : 0% (1)

In an initial experiment, the reaction between BH adduct **1a** and phenylboronic acid **2a** in the presence of $[Rh(cod)_2][PF_6]$ as catalyst in a mixture of toluene–water afforded unexpectedly alkene **3a** as the only reaction product and not the expected 1,4-addition adduct **4a** (eqn. (1)). As judged by NMR analysis, alkene **3a** was obtained in a stereoselective manner and was 95% of (*E*) stereochemistry. The reaction conditions were further optimized by a variation of catalyst or solvent. Among the tested catalysts, palladium complexes, which have been used in coupling reaction of BH acetates,[6] did not show any activity. Using ruthenium complexes, isomerization of the carbon–carbon double bound of **1a** is the dominant process, as observed to date.[14] It is only when using rhodium catalysts that alkene **3a** is produced in high yield. Particularly, commercially available $[Rh(cod)Cl]_2$ has proved to be highly suited in this reaction. Among the tested solvents, methanol appeared to be the solvent of choice, alkene **3a** being formed in less than 30 minutes at 50 °C with the highest isomeric ratio (99/1) in 90% yield. Finally, no loss of catalyst activity was observed when the reaction was conducted in open vessel without degassing the solvents (aerobic conditions). Furthermore, catalyst loading could be reduced to 1 mol% without loss of activity. Under these optimized conditions, that is 0.5 mol% $[Rh(cod)Cl]_2$ as catalyst in methanol at 50–55 °C, several alkenes were obtained in high yields and isomeric ratio from the reaction of arylboronic acids and BH adducts (Table 1). From these results it appeared that both aromatic and aliphatic BH adducts show similar reactivity,[15] the latter giving higher isomeric ratio (up to 99%). More generally, it seemed that increasing steric hindrance of the R^1 substituent resulted in a lower stereoselectivity and a slight decrease in reactivity. On the other hand, all the tested arylboronic acids reacted equally well. All these reactions, conducted under aerobic conditions, were completed in less than 30 minutes, proving the high efficiency of this catalytic system. It is also important to note that the reaction can be conducted in water as the sole solvent or at room temperature with comparable yields but longer reaction times.

Baylis–Hillman adducts, bearing allyl alcohols and activated alkenes moieties can either react *via* π-allyl type intermediate[16] or *via* 1,4-addition mechanism.[3d] To get further insight into the mode

Table 1 Aerobic rhodium-catalyzed addition of **2** to BH adduct **1**[a]



Entry	R^1	R^2	Yield[b] (%)	E/Z[c]
1	**1a**	Ph **2a**	90	99/1
2	**1a**	4-$CF_3C_6H_4$ **2b**	86	99/1
3	**1a**	4-$MeOC_6H_4$ **2c**	97	99/1
4	**1a**	1-naphthyl **2d**	92	99/1
5	**1a**	3-$CF_3C_6H_4$ **2e**	77	96/4
6	*n*-C_9H_{19} **1b**	2-naphthyl **2f**	92	97/3
7	**1b**	2-MeC_6H_4 **2g**	89	96/4
8	$(CH_3)_2CHCH_2$ **1c**	4-MeC_6H_4 **2h**	66	96/4
9	**1c**	**2a**	87	97/3
10	cyclohexyl **1d**	**2a**	32	90/10
11	1-naphthyl **1e**	**2a**	80	98/2
12	4-$NO_2C_6H_4$ **1f**	**2a**	86	96/4
13	4-ClC_6H_4 **1g**	**2a**	71	99/1

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), 0.5 mol% $[Rh(cod)Cl]_2$, 1 ml solvent at 50–55 °C. [b] Isolated yields. [c] *E*/*Z* ratio determined by GC/MS analysis.

† Electronic supplementary information (ESI) available: general methods. See http://www.rsc.org/suppdata/cc/b4/b402928c/

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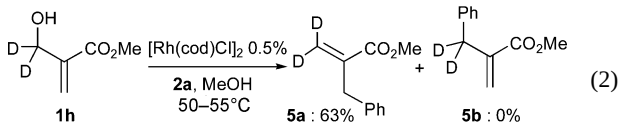
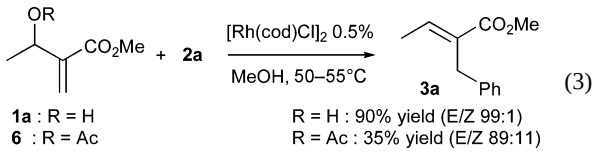
of reactivity of the BH adducts under the present conditions, deuterium-labeling experiments were undertaken using deuteriated **1h** as substrate. It was expected that the formation of a rhodium π-allyl type intermediate from **1h** would lead to the formation of a 50:50 mixture of alkenes **5a** and **5b**. Surprisingly, reaction of **1h** (> 95% deuteriated) with **2a** in the presence of 0.5 mol% of $[Rh(cod)Cl]_2$ in methanol at 50 °C for 5 minutes led to the exclusive formation of **5a** (> 95% deuteriated) in 63% yield (eqn. (2)).



(2)

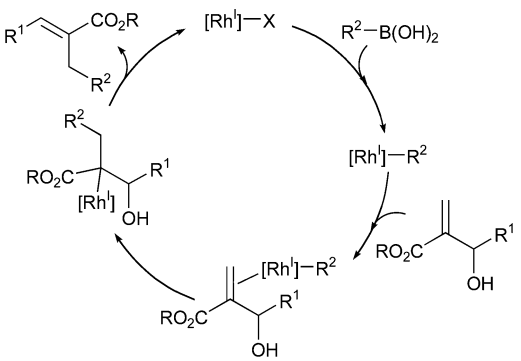
This high regioselectivity of the reaction cannot be explained by a π-allyl type mechanism but rather by a 1,4-addition type mechanism. The intervention of a π-allyl type intermediate was further excluded given the very low reactivity of the acetate of BH adduct **6**. Indeed, under the described conditions, reaction of compound **6** with phenylboronic acid **1a** show lower efficiency compared to free BH adduct **1a** (35% yield after 2 h) and very low stereoselectivity (*E*/*Z* 89:11) was observed (eqn. (3)).



(3)

To explain this high regioselectivity and the higher reactivity of unactivated BH adducts, a 1,4-addition type mechanism involving a β-hydroxy elimination step[17] may be postulated. The initial step of the catalytic cycle should consist in the transmetallation of the organoboron reagent $R^2B(OH)_2$ to [Rh(I)] species followed by coordination of the BH adduct (Scheme 1). 1,4-insertion of the organic substituent R^2 affords a rhodium intermediate bearing a hydroxy in the β-position. The last step of the mechanism should involve a syn β-hydroxy elimination[17] of [Rh]–OH allowing the formation of the alkene **3**. The catalytic cycle can continue further because of the ease of transmetallation of arylboronic acids to [Rh]–OH.[18] At present we have not have studied the origin of the high stereoselectivity, but we can guess that it arises from steric interaction during the β-hydroxy elimination step.

We have thus described a highly efficient process allowing access to stereodefined trisubstituted alkenes involving an unusual mode of reactivity: the rhodium catalyzed 1,4-addition/β-hydroxy elimination. This reaction presents several attractive features, not only because of the operating conditions (low temperature, aerobic conditions) but also because of the easily accessible BH adduct as starting material.



Scheme 1 Proposed mechanism.

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