Anti-Markovnikov hydroarylation of styrenes catalyzed by an *in situ* generated ruthenium complex†

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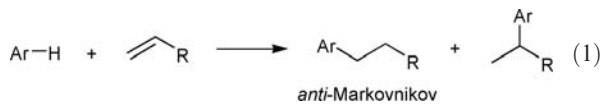
An efficient and practical catalytic system for the *anti*-Markovnikov ruthenium-catalyzed hydroarylation of styrenes with acetophenone, allowing a straightforward access to bibenzyl backbones, is described for the first time: this process, involving regioselective C–H bond activation, is complementary to a Friedel–Crafts type reaction giving the branched adduct.

Transition metal-catalyzed C–H bond activation towards C–C bond formation[1] are highly desirable processes in organic synthesis as they fulfil atom economy concepts.[2] Among them, hydroarylation of alkenes constitutes a powerful tool for the functionalization of aromatic rings. The Lewis acid or transition metal-catalyzed Friedel–Crafts reaction involving the coupling between arenes and alkenes is one of the widely used examples of hydroarylation reaction.[3,4] Involving the activation of the olefin through a carbocationic species, they are leading to alkylated arenes in a Markovnikov fashion (branched product, eqn (1)).

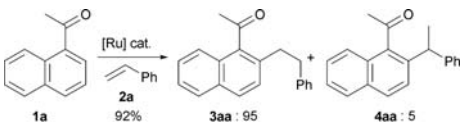


Several products showing biological activities have a bibenzylic moiety and thus cannot be obtained by Friedel–Crafts alkylations. They are usually prepared by, either Friedel–Crafts acylation followed by reduction of the carbonyl moiety to methylene, or by palladium-catalyzed Heck or Sonogashira reactions followed by hydrogenation of the resulting C–C mutliple bond.[5] But these multistep processes are time consuming and are not satisfying from an atom economy approach.[2]Formation of bibenzyl backbones *via anti*-Markovnikov hydroarylation processes involving C–H bond activation would be highly desirable.[6] However, such reactions have been scarcely described in the literature: a lack of selectivity for the *anti*-Markovnikov product is generally observed and the generality has not been proven.[7] For example, in the presence of an iridium catalyst, Periana and Matsumoto obtained bibenzyl from benzene and styrene with a high *anti*-Markovnikov regioselectivity, but the generality of the reaction was not proven.[7c,e] Murai and co-workers described a ruthenium-catalyzed hydroarylation of styrenes, but the reaction generally suffered from a lack of selectivity and the use of more sterically hindered styrenes, such as 2-methylstyrene, was necessary to obtain high proportions of the linear product.[7a]

We recently reported the use of an *in situ* generated ruthenium complex for C–C bond formation *via* C–H bond activation and particularly in Murai's type of reaction.[8] One of the main interest of this catalytic system, compared to other catalyst for C–H bond activation,[1] was the possibility of tuning the ligand depending on the substrates. Taking advantage of this versatility, we want to report here an efficient and general catalytic system for the selective *anti*-Markovnikov hydroarylation of styrenes.

The feasibility of the reaction was initially studied using 1-acetonaphthone (**1a**) and styrene (**2a**) as model substrates with an *in situ* generated ruthenium catalyst made up of dimeric [Ru(*p*-cymene)Cl_2]$_2$ associated with sodium formate and phosphorous ligands (Scheme 1). Among the tested phosphanes, a 92% yield and high selectivity (95%) for the linear product **3aa** was achieved using the sterically hindered dicyclohexylphenylphosphane.[9]

However, disappointing results were obtained when extending these conditions to other acetophenone derivatives. Indeed, although the selectivity for the *anti*-Markovnikov product remains elevated (>99%) in the reaction of 4-methylacetophenone (**1b**) with styrene (**2a**), the conversion drops dramatically to only 5% (Table 1, entry 3). This result prompted us to further investigate the catalytic system, particularly the phosphane ligand, in order to find more suitable conditions for the reaction of acetophenone derivatives with styrenes (Table 1). Among the tested phosphane ligands, only monodentate tri-arylphosphanes afforded the expected hydroarylation adduct in acceptable yields and, as observed in the case of vinylsilane,[12] the reaction was very sluggish using bidentate phosphane ligands. Moreover, it does seem that both the steric and electronic nature of the ligand play a crucial role either in the conversion or in the observed selectivities. Indeed, increasing steric hindrance around the ruthenium center resulted in an increase of *anti*-Markovnikov selectivity (entries 1–4 and 11), while conversion dropped



Scheme 1 Ruthenium-catalyzed hydroarylation of styrene with **1a**.

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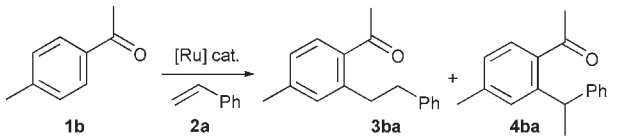
Table 1 Screening of phosphane ligands for the reaction of 4-methylacetophenone (**1b**) with styrene (**2a**)[a]



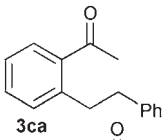
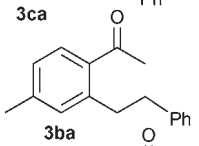
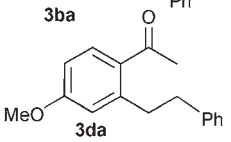
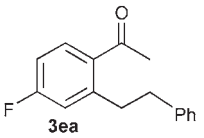
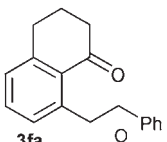
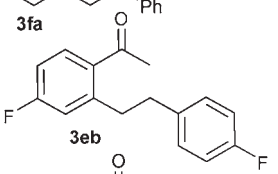
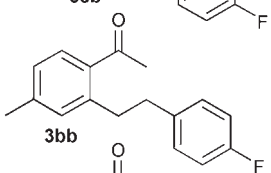
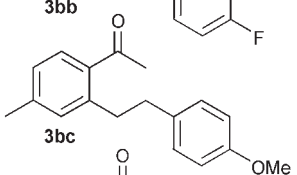
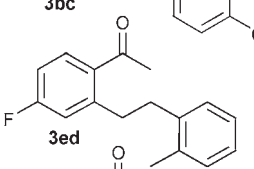
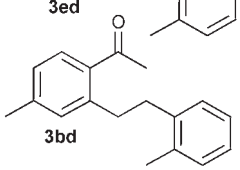
Entry	Ligand	% Yield[b]	**3ba**/**4ba**[c]
1	PPh_3	90	86 : 14
2	$PCyPh_2$	13	92 : 8
3	PCy_2Ph	5	100 : 0
4	PCy_3	7	100 : 0
5	$PMePh_2$	41	36 : 64
6	PMe_2Ph	17	17 : 83
7	P(*m*-tolyl)$_3$	39	86 : 14
8	P(*o*-tolyl)$_3$	0	—
9	P(4-$MeOC_6H_4$)$_3$	82	87 : 13
10	P(4-$CF_3C_6H_4$)$_3$	93	93 : 7
11	P[3,3-$(CF_3)_2C_6H_3$]$_3$	8	95 : 5
12	P(2-furyl)$_3$	7	75 : 25

[a] Reactions conducted with 1 mmol of **1b**, 2 equiv. of **2a**, 2.5 mol% of [Ru(*p*-cymene)Cl_2]$_2$, 30 mol% $NaHCO_2$ and 15 mol% of ligand, at 140 °C in 1 mL toluene. [b] Yield after 20 h determined by GC using an internal standard. [c] Proportion of regio-isomers product determined by GC.

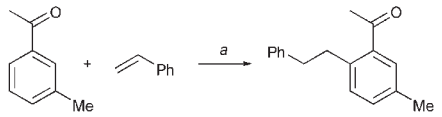
dramatically. On the other hand, the use of phosphane ligand with lower Tolman angle[10] (entries 1, 5–6) completely reversed the selectivity. For example, the reaction conducted in the presence of PMe_2Ph afforded the Markovnikov hydroarylation adduct **4ba** with 83% selectivity. Among the tested triarylphospanes, we were pleased to find that high yields and selectivities were achieved using *tris*-[(trifluoromethyl)phenyl]phosphane as the ligand (entry 10). It is also important to note that the amount of phosphane ligands, compared to ruthenium, only influences the conversions whereas the selectivities remain unchanged. For example, under identical conditions, but using only two equivalents of *tris*[(trifluoromethyl)phenyl]phosphane compared to ruthenium, the conversion was only of 50% while the linear hydroarylation adduct **3ba** was formed with 92% selectivity.

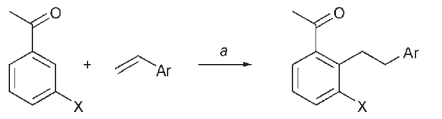
The generality of the optimized conditions for the *anti*-Markovnikov hydroarylation of styrene derivatives using the *in situ* generated ruthenium catalyst was evaluated on various acetophenones and styrenes (Table 2). With all the examined substrates, high yields and regioselectivities were generally achieved whatever the substitution patterns on the substrates. The electronic nature of the substituents on the arylketone did not seem to influence neither the yields nor the selectivities, and, the *anti*-Markovnikov adducts were generally obtained with more than 91% selectivity. With some arylketones, particularly 4-fluoro-substituted ones, *ortho*-disubstituted products, resulting from two subsequent hydroarylation processes, were also formed, and this disubstituted adduct was merely 100% linear (entries 4, 6, 9 and 10). A slightly lower selectivity was observed using α-tetralone (**1f**), an *ortho*-substituted ketone (entry 5). Other styrenes participated in the reaction and the anti-Markovnikov adducts were obtained with selectivities ranging from 92 to 99% (entries 6–10). Steric hindrance of the styrene moiety resulted in an increase of the proportion of the linear adduct, and hydroarylation of 2-methylstyrene (**2d**) afforded only one isomer in a quantitative yield (entries 9 and 10).[11]

Table 2 *Anti*-Markovnikov hydroarylation of styrenes with an *in situ* generated ruthenium catalyst[a]

Entry	Product	Yield[b] (%)	Selectivity[c] (%)
1	 **3ca**	99	92
2	 **3ba**	100	94
3	 **3da**	71	92
4	 **3ea**	87[d]	91
5	 **3fa**	68	89
6	 **3eb**	99[d]	97
7	 **3bb**	83	92
8	 **3bc**	85	92
9	 **3ed**	100[d]	>99
10	 **3bd**	100[d]	>99

[a] Reactions conducted with 1 mmol of aromatic ketone, 2–4 equiv. of **2**, 2.5 mol% of [Ru(*p*-cymene)Cl_2]$_2$, 30 mol% HCO_2Na and 15 mol% of P(4-$CF_3C_6H_4$)$_3$, at 140 °C in 1 mL toluene. [b] Isolated yields of hydroarylation products. [c] Proportion of *anti*-Markovnikov product determined by ^{1}H NMR. [d] Total yield taking into account the presence of dihydroarylation adduct (from 10 to 30%).





[a] Reactions conducted with 1 mmol of ketone, 2 equiv. of **2a** or **2b** (Ar = 4-FC_6H_4), 2.5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$, 30 mol% HCO_2Na and 15 mol% of ligand, at 140°C in 1mL toluene. [b] Isolated yields: between parenthesis, % of linear product determined by GC/MS and ^1H NMR.

Scheme 2 Regioselectivity of the ruthenium-catalyzed hydroarylation.

Interesting regioselectivities were also achieved with *meta*-substituted acetophenones, not only concerning the hydroarylation process (linear/branched adducts) but also concerning the selectivity of the C–H bond activation process (Scheme 2). Indeed, in the case of 3-methylacetophenone (**1g**), among the four possible isomers, the less hindered position of the arylketone was selectively functionalized and the hydroarylation adduct **3ga** was obtained in quantitative yield with 95% *anti*-Markovnikov selectivity. On the other hand, with a ketone bearing a complexing substituent (fluorine or methoxy) in the *meta* position, the most hindered position was selectively activated and the linear adducts **3ha**, **3hb** and **3ia** were produced in good yields (62–92%) and very high selectivities (96–97%).[12] These linear to branched selectivities and C–H bond functionalisation regioselectivities are different and complementary to Friedel–Crafts reactions where the less hindered position is generally functionalized in a Markovnikov manner.[3,4]

Indeed, we have developed an efficient and practical catalytic system for the *anti*-Markovnikov hydroarylation of styrene derivatives, allowing a straightforward access to bibenzyl backbones. Thanks to a fine-tuning of the ligands around the ruthenium center, high selectivities were attained in favor of the linear adduct, allowing the functionalisation of various substrates. This process, which is complementary to Friedel–Crafts type reaction, should be useful in organic synthesis.

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9 See supporting information for a screening of ligands using 1-acetylnaphthalene. Under identical conditions, low selectivities were achieved using Murai catalyst $RuH_2(CO)(PPh_3)_3$ (l/iso 48 : 52)†.

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