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A Simple Catalyst for the Efficient Benzylation of Arenes by Using Alcohols, Ethers, Styrenes, Aldehydes, or Ketones

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Abstract: The compound $[IrCp^*(OTf)_2(I^{nBu})]$ $(I^{nBu}=1,3-di-n-butyl-imidazolylidene)$ is an effective catalyst in the benzylation of arenes with different benzylating agents, such as alcohols, ethers and styrenes, representing an unprecedented highly versatile catalyst for this type of process. The same compound also catalyses a remarkable tandem process that allows the use of aldehydes and ketones as benzylating agents, through the base-free hydrogenation of C=O bonds with *i*PrOH and further use of the resulting primary or secondary alcohols as benzylating agents.

Introduction

The functionalisation of arenes is an important tool toward the preparation of highly valuable chemicals of industrial relevance. The typical procedures for this type of transformation imply the use of traditional Friedel–Crafts reactions, in which alkyl halides and Lewis acid catalysts are utilised.^[1] These conditions, however, afford the concomitant production of hydrogen halides that often induce side reactions and many byproducts. As an alternative, recent reports have proposed the use of alcohols,^[2–4] ethers,^[5,6] styrenes^[7,8] or benzylic acetates^[9] for which milder reaction conditions are needed and side reactions are avoided.

In the search for new catalytic systems capable to afford the functionalisation of arenes, it is not only desirable to have a catalyst with high activity and selectivity, but also that its versatility widens the scope of substrates able to afford the final products. Simple catalysts that are able to facilitate multistep processes may also lead to a wider library of potential useful products. In this sense, most Lewis acid catalysts used in the traditional Friedel–Crafts processes are able to catalyse only one or two specific reactions, thus limiting their scope.

We have recently described a series of $[IrCp^*(NHC)]$ complexes (NHC=N-heterocyclic carbenes) that have shown excellent activity in a wide set of C-H activation pro-

 [a] A. Prades, Dr. R. Corberán, Dr. M. Poyatos, Prof. E. Peris Departamento de Química Inorgánica y Orgánica Universitat Jaume I, 12071-Castellón (Spain) Fax: (+34)964-72-82-15 E-mail: eperis@qio.uji.es cesses.^[10–13] The versatility of such catalysts can be exemplified by the fact that the same compound is capable of dehydrogenating alcohols, coupling alcohols to form ethers, and allows all three possible cross-coupling combinations between amines and alcohols, depending on the reaction conditions used.^[13] We now show that the same compound is an effective catalyst in the benzylation of arenes with alcohols, ethers and styrenes, and also catalyses a remarkable tandem process that allows the unprecedented use of aldehydes and ketones as benzylating agents.

reactions

Keywords: arenes • benzylation •

hydroarylation • hydrogen transfer •

N-heterocyclic carbenes • tandem

Results and Discussion

In first place, we studied the different activities of several $Ir-Cp^*$ complexes (1-3) in the benzylation of toluene using



benzyl alcohols (Table 1). We observed that all NHC containing complexes of the type $[IrCp^*(OTf)_2(NHC)]$ showed a higher activity than that shown by $[{IrCp^*Cl_2}_2]/AgOTf$. From all, $[IrCp^*(OTf)_2(I^{nBu})]$ (1: $I^{nBu} = 1,3$ -di-*n*-butyl-imidazolylidene) was the one to show better catalytic activities.

The direct use of **1** or its in situ preparation from $[IrCp*Cl_2(I^{nBu})]$ and addition of an excess of AgOTf,^[10] did





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Table 1. Comparison of the different catalysts towards benzylation of toluene using benzyl alcohol.^[a]



[a] Reaction Conditions: benzyl alcohol (3 mmol), toluene (15 mmol), catalyst (0.003 mmol, 0.1 mol%). Yields determined by ¹H NMR spectroscopy.

not lead to any significant differences in the catalytic activities shown.

We then used 1 in a series of reactions in which different benzylating agents were used for the functionalisation of several arenes. Table 2 shows the catalytic results when

Table 2. Benzylation of arenes with catalyst 1.^[a]



R'= H, Me; R-=H, Bh

	Benzylating agent	Arene	Cat. loading [%]	<i>t</i> [h]	Yield [%]	Ratio <i>o:p</i>
1	benzyl alcohol	toluene	0.1	3	>95(89) ^[b]	35:65
2	benzyl alcohol	anisole	0.1	3	>95	35:65
3	benzyl alcohol	benzene	0.1	6	75	-
4	benzyl alcohol	o-xylene	0.1	3	>95	35:65
5	benzyl alcohol	p-xylene	0.1	3	$> 95(89)^{[b]}$	-
6	1-phenyl ethanol	toluene	0.1	4	32	10:90
7	1-phenyl ethanol	anisole	0.1	3	>95	10:90
8	1-phenyl ethanol	p-xylene	0.1	4	40	10:90
9	1-phenyl ethanol	phenol	0.1	4	>95	40:60
10	dibenzyl ether	toluene	1	6	>95(90) ^[b]	35:65
11	dibenzyl ether	anisole	1	5	>95	35:65

[a] Reaction Conditions: Benzylating agent (1 mmol), arene (5 or 10 mmol) and catalyst (1 or 0.1 mol%). Yields determined by ¹H NMR spectroscopy. [b] Isolated yields.

benzyl alcohol, 1-phenyl ethanol and dibenzyl ether are used. As can be seen from the results shown, a catalyst loading as low as 0.1 mol%, affords high to excellent conversions at short reaction times (3-4 h) when both alcohols were used (Table 2, entries 1–9). The benzylation of benzene required a longer reaction time, and a maximum yield of 75% was achieved. Poor selectivities in the production of the *ortho/para* isomers were obtained when benzyl alcohol was used (entries 1, 2 and 4), although they improved when the higher steric demanding 1-phenyl ethanol was utilised (entries 6–8). The reactions carried out with dibenzyl ether required a higher catalyst loading of 1 mol% and longer reaction times, although they also afforded full conversions to the final products (entries 10 and 11). These data compare well and even improve the results obtained for other recently used transition-metal catalysts for the benzylation of arenes with benzyl alcohols, in which higher catalyst loadings and longer reaction times were needed.^[4,5]

Direct addition of styrenes to arenes (also known as hydroarylation of styrenes) has recently appeared as an interesting alternative for the preparation of 1,1-diarylarenes.^[7,8] As shown by the data presented in Table 3, compound **1**





	Styrene	Arene	Cat. loading [%]	<i>t</i> [h]	Yield [%]	Ratio <i>o:p</i>
1	styrene	toluene	1	6	30	10:90
2	styrene	anisole	0.1	4	$> 95^{[b]}$	10:90
3	styrene	phenol	1	4	>95	40:60
4	4-chloro styrene	anisole	1	4	>95	15:85
5	1,2-dihydro naphthalene	anisole	0.1	4	>95	10:90
6	indene	anisole	0.1	4	>95	25:75

[[]a] Reaction Conditions: Styrene derivative (1 mmol), arene (5 mmol) and catalyst (1 or 0.1 mol%). Yields determined by ¹H NMR spectroscopy. [b] Isolated yield 87%.

displayed an excellent activity in this type of reaction. Except for the case of the benzylation of toluene (Table 3, entry 1), the catalyst showed high activity for all other combinations of arenes and styrenes. Remarkably, in the case of the benzylation of anisole, catalyst loadings as low as 0.1 mol% afforded full conversions in only 4 h under the reaction conditions used. In most cases the reaction proceeds with a high selectivity to the *para* isomers.

We also performed an experiment implying the coupling of styrene and $[D_8]$ anisole, in which we clearly observe that the deuterium from the anisole selectively moves to the methyl group of the ethyl bridge in the final product (Scheme 1), so that the reaction can be regarded as an insertion of the molecule of styrene in one of the C–D bonds in a Markovnikov fashion. It has been proposed that the mechanism for this reaction operates through a metal-mediated electrophilic aromatic substitution,^[8] but a mechanism implying the oxidative addition of a C–D bond of the anisole to the Ir centre and further insertion of the olefin in the Ir–D bond cannot be discarded. This result is also interest-



Scheme 1. Reaction of styrene with [D₈]anisole.

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ing because we did not detect any further scrambling of deuterium about the molecule as a consequence of any other C–H associated processes, considering that **1** also proved to be a highly efficient catalyst in H/D exchange reactions.^[12]

Compound **1** also catalysed the benzylation of anilines with styrenes, as shown in Table 4, providing results that compare well with those previously reported which made use of Brønsted acids^[14,15] or metal complexes^[16,17] as catalysts.



[a] Reaction Conditions: Styrene (1 mmol), aniline derivative (5 mmol) and catalyst (1 mol%). Yields determined by ¹H NMR spectroscopy. [b] N-alkylation products.

p-chloroaniline

p-methoxyaniline

95

50

90:10:-

83:17:-

The fact that **1** is also very active in many other metalmediated catalysed reactions, prompted us to carry out a tandem process for which standard Friedel–Crafts catalysts would be ineffective. In this sense, we carried out the reaction of benzaldehyde or acetophenone with anisole in the presence of **1** and *i*PrOH, as shown in Table 5. It is important to point out that only 1.5 equivalents of *i*PrOH were needed in order to facilitate the reduction of the carbonyl group of the aldehyde or ketone. The reaction provided full conversions to the final benzylated products. Remarkably, this catalytic tandem process gathers two different reactions for which **1** has shown excellent activities, namely, the reduction of aldehydes and ketones with *i*PrOH through hydrogen transfer,^[10] and the benzylation of the arene with the resulting alcohol.

Table 5. Tandem reaction-reduction of alcohol and benzylation.^[a]



 2
 acetophenone
 >95
 10:90

 [a] Reaction Conditions: Benzylating agent (1 mmol), anisole (10 mmol), *iPrOH* (1.5 mmol) and catalyst (1 mol%). Yields determined by ¹H NMR spectroscopy. [b] Isolated yield.

benzaldehvde

 $> 95(88)^{[b]}$

35:65

Conclusion

Although a wide variety of Lewis acids and transition-metal complexes have been used to catalyze the Friedel-Crafts benzylation, there are always limitations of the structure of the benzylation reagents. In this work, we proved that complex 1 is an efficient catalyst for a wide set of benzylation reactions, for which different benzylating agents such as alcohols, ethers and styrenes have been used, confirming the wide applicability of this catalyst. All the reactions constitute valuable processes for the preparation of biologically active species and industrial chemicals. The fact that 1 is also an excellent catalyst in hydrogen transfer processes allowed us to carry out an unprecedented tandem reaction, implying the reduction of aldehydes or ketones to alcohols, which are further used as benzylating agents of arenes. This latter process can be carried out with a minimum amount of iPrOH as reducing agent, thus implying that the overall reperformed under environmentally benign action is conditions.

Experimental Section

General procedures: [{IrCp*Cl₂]₂] was prepared according to literature methods.^[18] [IrCp*Cl₂(NHC)] complexes (NHC=1,3-di-*n*-butyl-imidazol-2-ylidene,^[12] 1,2,3-trimethyl-imidazol-4-ylidene^[19] and 1,2-dimethyl-pyrazol-3-ylidene^[13]) were prepared as previously reported by us. The catalytic experiments were performed either by the direct use of the isolated bistriflate complexes^[10] or their in situ generation from the dichloro compounds and addition of an excess of AgOTf. All other reagents were used as received from commercial suppliers and used without further purification. For the isolation of the products of the catalytic experiments are extracted with dichloromethane and filtrated through a pad of Celite. The solvent was removed under vacuum, and the crude solid purified by flash chromatography on silica gel using hexanes as eluent. NMR spectra were recorded on a Varian Innova 300 MHz and 500 MHz, using CDCl₃ as solvent.

Catalytic experiments

Benzylation of arenes: A mixture of benzylating agent (1 mmol), arene (5 or 10 mmol), catalyst (0.1 or 1 mol%) and silver triflate (0.3 or 3 mol%) was heated at 110 °C in a thick-walled glass tube fitted with a Teflon cap. The reaction mixture was analysed by ¹H NMR spectroscopy and yields calculated based on the amount of arene.

Reaction of styrene derivatives with arenes: A mixture of styrene derivative (1 mmol), arene (5 mmol), catalyst (0.1 or 1 mol%) and silver triflate (0.3 or 3 mol%) was heated at 110°C in a thick-walled glass tube fitted with a Teflon cap. The reaction mixture was analysed by ¹H NMR spectroscopy and yields calculated based on the amount of arene. Products of the benzylation of arenes were identified according to previously reported spectroscopic data: 2- and 4-(methylphenyl)phenylmethane,^[5] 2- and 4-(methoxyphenyl)phenylmethane,^[3] diphenylmethane,^[3] 2,3- and 3,4-(dimethylphenyl)phenylmethane,^[3] 2,5-(dimethylphenyl)phenylmethane,^[3] 1methyl-2-(1-phenylethyl)benzene and 1-methyl-4-(1-phenylethyl)benzene,^[7] 1-methoxy-2-(1-phenylethyl)benzene and 1-methoxy-4-(1-phenylethyl)benzene,[7] 1,4-dimethyl-2-(1-phenylethyl)benzene,[7] 2- and 4-(1phenylethyl)phenol,^[7] 1-chloro-4-(1-(2-methoxyphenyl)ethyl)benzene and 1-chloro-4-(1-(4-methoxyphenyl)ethyl)benzene,^[7] 1-(2-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene and 1-(4-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene,[7] 1-(2-methoxyphenyl)-2,3-dihydro-1H-indene and 1-(4methoxyphenyl)-2,3-dihydro-1H-indene.[7]

Reaction of styrene with aniline derivatives: A mixture of styrene (1 mmol), aniline derivative (5 mmol), catalyst (1 mol%) and silver trif-

1

5

6

late (3 mol%) was heated at 150 °C in a thick-walled glass tube fitted with a Teflon cap. The reaction mixture was analysed by ¹H NMR spectroscopy and yields calculated based on the amount of arene. Products were identified according to previously reported spectroscopic data: 2-(1-phenylethyl)benzenamine and 4-(1-phenylethyl)benzenamine, N-(1-phenylethyl)benzenamine, ^[20] 2-methyl-6-(1-phenylethyl)benzenamine and 2-methyl-4-(1-phenylethyl)benzenamine, ^[14] α -methyl-N-(2-methylphenyl)benzenemethanamine, ^[21] 4-methyl-2-(1-phenylethyl)benzenamine, α -methyl-N-(4-methylphenyl)benzenemethanamine, 4-fluoro-2-(1-phenylethyl)benzenemethanamine, ^[17] 4-chloro-2-(1-phenylethyl)benzenemethanamine, ^[17] 4-chloro-2-(1-phenylethyl)benzenemethanamine, ^[17] 4-chloro-2-(1-phenylethyl)benzenemethanamine, ^[22] 4-methoxy-2-(1-phenylethyl)benzenemethanamine, ^[21] 4-methoxy-2-(1-phenylethyl)benzene

Tandem reaction: A mixture of benzylating agent (1 mmol), anisole (10 mmol), *i*PrOH (1.5 mmol), catalyst (1 mol%) and silver triflate (3 mol%) was heated at 110 °C in a thick-walled glass tube fitted with a Teflon cap. The reaction mixture was analysed by ¹H NMR spectroscopy and yields calculated based on the amount of arene.

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