ACS Catalysis

Letter

pubs.acs.org/acscatalysis

Osmium Catalyst for the Borrowing Hydrogen Methodology: α-Alkylation of Arylacetonitriles and Methyl Ketones

María L. Buil,[†] Miguel A. Esteruelas,[†,*] Juana Herrero,[§] Susana Izquierdo,[†] Isidro M. Pastor,[‡] and Miguel Yus[‡,*]

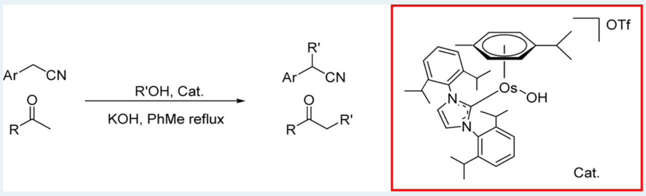
[†]Departamento de Química Inorgánica, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain

[§]Departamento de Ingeniería Química y Química Inorgánica, ETSIIYT, Universidad de Cantabria, 39005 Santander, Spain

[‡]Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Supporting Information

ABSTRACT: Complex [Os(η^6-p-cymene)(OH)(IPr)]OTf is an efficient catalyst precursor for the α-alkylation of arylacetonitriles and methyl ketones with alcohols, which works with turnover frequencies between 675 and 176 h^{-1} for nitriles and between 194 and 28 h^{-1} for ketones.

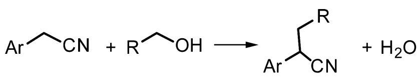


KEYWORDS: *osmium, borrowing hydrogen, hydrogen autotransfer, nitriles alkylation, ketones alkylation*

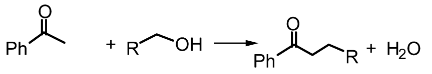
The development of the borrowing hydrogen methodology,[1] also called hydrogen autotransfer,[2] is a challenge for the modern chemistry from an economical and environmental point of view, since it provides a useful alternative to conventional alkylation reactions for the formation of C−C bonds and the only waste generated through the overall process is water. Catalysts temporarily remove hydrogen from an alcohol substrate to provide an aldehyde or ketone intermediate, which readily undergoes alkene formation. Return of the hydrogen leads to an overall redox neutral process.

Key reactions involving C−C formation proceeding through a borrowing hydrogen pathway include α-alkylation of nitriles and ketones, the α-alkylation of nitriles being less studied. One of the earliest examples using homogeneous catalysis involved the Ru-promoted α-alkylation of aryl acetonitriles, reported by Grigg and co-workers in 1981.[3] Subsequently, this group[4] and Obora[5] described the use of iridium catalysts. Dialkylaminocyclopentadienylruthenium(II) complexes,[6] Ru-grafted hydrotalcite,[7] and hydrotalcite-supported Pd nanoparticles[7b] have also been shown to be efficient. Although the α-alkylation of ketones has been slightly more studied than that of nitriles, the catalysts used are also based on few transition metals: Ru,[8] Ir,[9] and Pd,[10] as in the nitrile case. Here, we report the first osmium catalyst, which is more efficient than those previously studied, in particular for the α-alkylation of aryl acetonitriles.

Osmium has been traditionally used to prepare stable models of reactive intermediates proposed in reactions catalyzed by ruthenium analogous,[11] whereas its use in catalysis has received scarce attention.[12] Recent findings have, however, demonstrated that osmium is certainly a promising alternative to the classical metal catalysts for promoting some organic reactions.[13] In agreement with this, we reported the first osmium−N-heterocyclic carbene (NHC) catalysts in 2005,[14] [Os(η^6-*p*-cymene)Cl(═CHPh)IPr]OTf and [Os(η^6-*p*-cymene)Cl(═CHPh)IMes]OTf (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazolylidene, IMes = 1,3-bis(2,4,6- trimethylphenyl)-imidazolylidene; OTf = CF_3SO_3).[15] They are active in the ring-closing metathesis of diallyl diethylmalonate, the ring-opening metathesis polymerization of cyclooctene, and a variety of olefin cross-metatheses. Following this report, we subsequently synthesized [Os(η^6-*p*-cymene)(OH)IPr]OTf (**1**), which was found to be an efficient catalyst precursor for the hydrogen transfer reaction from 2-propanol to numerous aromatic and aliphatic aldehydes[16] and for the hydration of a wide range of nitriles to amides.[17] Now, we have observed that this complex can be used in the borrowing hydrogen methodology to promote the α-alkylation of arylacetonitriles (eq 1) and methyl ketones, mainly acetophenone (eq 2).



(1)



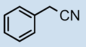
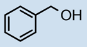
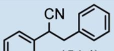
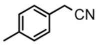
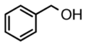
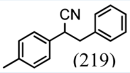
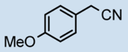
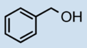
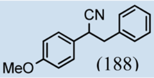
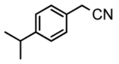
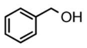
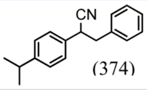
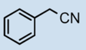
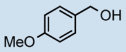
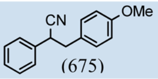
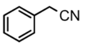
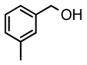
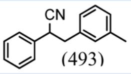
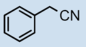
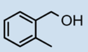
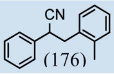
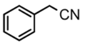
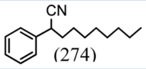
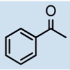
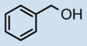
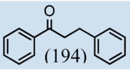
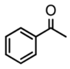
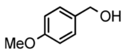
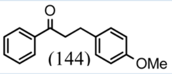
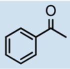
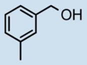
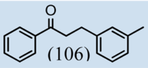
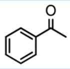
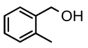
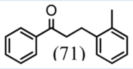
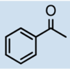
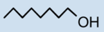
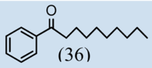
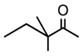
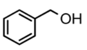
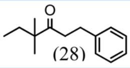
(2)

The alkylations of arylacetonitriles were performed in toluene under reflux, using nitrile and alcohol concentrations of 0.3 M and catalyst/substrate and KOH/substrate molar

Received: July 10, 2013
Revised: July 26, 2013

ratios of 1/100 and 1/5, respectively. Because complex **1** is also a very efficient catalyst for the hydration of nitriles to amides, the water generated during the process was removed from the reaction medium by using a Dean–Stark receiver filled with toluene. Under these conditions, the alkylation products are obtained in high yield within a short time in all cases, with turnover frequency values at 50% conversion (TOF$_{50\%}$), which ranges from 675 to 176 h^{-1} (Table 1).

Table 1. *α*-Alkylation of Arylacetonitriles and Methyl Ketones

Run	Substrate	Alcohol	Product (TOF$_{50\%}$,h^{-1})^b	t (h)	Yield (%)^c
1			 (514)	0.5	98
2			 (219)	0.75	93
3			 (188)	1	91
4			 (374)	0.75	98
5			 (675)	0.5	95
6			 (493)	0.5	97
7			 (176)	0.75	90
8			 (274)	1.5	79
9			 (194)	1.5	99
10			 (144)	2.25	94
11			 (106)	3	92
12			 (71)	6	91
13			 (36)	3	62
14			 (28)	4	78

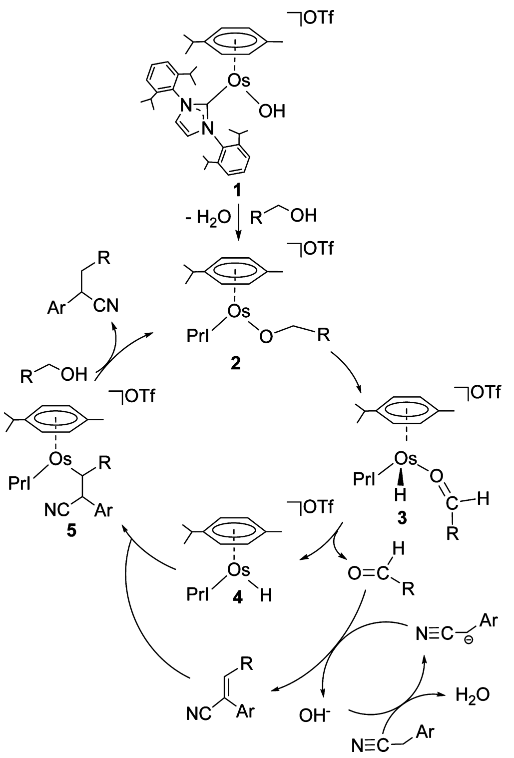
^{a}Reactions performed in toluene under Ar atmosphere at 110 °C using 3 mmol of the corresponding substrate (0.3 M). Os/substrate ratio: 0.01. KOH/substrate ratio: 0.2 using pentadecane as internal reference. ^{b}Turnover frequencies [(mol product/mol Os)/time] were calculated at 50% conversion. ^{c}Yields determined by ^{1}H NMR spectra.

The alkylation of phenylacetonitrile with benzyl alcohol in the presence of **1** is significantly faster than in the presence of the iridium dimer [IrCp*Cl$_2$]$_2$, even when the latter is used under microwave irradiation.[4] Although the osmium catalyst works with a TOF$_{50\%}$ of 514 h^{-1} (run 1), the iridium system affords only less than 2 h^{-1} under traditional heating and about 100 h^{-1} under microwave irradiation. Electron-donating substituents at the para position of the aromatic ring of the nitrile slow down the reaction (runs 2–4). In agreement with this, the TOF$_{50\%}$ values for the alkylation of 4-substituted phenylacetonitriles decrease in the sequence H > Me > MeO; however, electron-donating substituents at the para position of the phenyl group of benzyl alcohol increase the alkylation rate. Thus, with (*p*-methoxyphenyl)methanol, a TOF$_{50\%}$ value of 675 h^{-1} is reached (run 5). The position of the substituent of the aromatic group of benzyl alcohol also has a clear influence on the reaction rate, increasing it because the substituent is away from the functional CH$_2$OH (runs 6 and 7). According to this, the TOF$_{50\%}$ value for the alkylation of phenylacetonitrile with *m*-tolylmethanol is higher than that for the reaction involving *o*-tolylmethanol (493 vs 176 h^{-1}). Less reactive aliphatic alcohols are also efficient alkylation agents. Thus, the alkylation of phenylacetonitrile with octan-1-ol takes place with a high TOF$_{50\%}$ value of 274 h^{-1} (run 8).

Complex **1** is also the most efficient homogeneous catalyst reported until now for the *α*-alkylation of acetophenone, although the obtained TOF$_{50\%}$ values, which range from 194 to 36 h^{-1}, are significantly lower than those found for the reactions with nitriles (Table 1). Under the conditions used for the latter, the obtained ketones are formed in high yields after a few hours, whereas more than 20 h is necessary to reach similar yields with Ru, Ir, and Pd catalyst.[8−10] In contrast to the *α*-alkylation of phenylacetonitrile, electron-donating substituents at the para position of the aromatic ring of benzyl alcohol slow down the reaction (runs 9 and 10). Thus, the reaction with benzyl alcohol (TOF$_{50\%}$ = 194 h^{-1}) is faster than that with *p*-methoxybenzyl alcohol (TOF$_{50\%}$ = 144 h^{-1}). In this case, the position of the substituent at the phenyl group of the alcohol also has a marked influence on the rate and, similar to the *α*-alkylation of phenylacetonitrile, it increases because the substituent is away from the CH$_2$OH group (runs 11 and 12). In accordance with this, the TOF$_{50\%}$ value for the alkylation with *m*-tolylmethanol (106 h^{-1}) is higher than that for the reaction with *o*-tolylmethanol (71 h^{-1}). The alkylation with the aliphatic octan-1-ol is also efficient (run 13), although the TOF$_{50\%}$ value of 36 h^{-1} is significantly lower. Complex **1** alkylates not only acetophenone but also aliphatic ketones. Thus, the alkylation of 3,3-dimethylpentan-2-one with benzyl alcohol takes place in high yield with a TOF$_{50\%}$ of 28 h^{-1}.

The hydroxo ligand of **1** is easily replaced by an alkoxide group. In methanol at −30 °C, complex **1** evolves into the methoxide derivative [(η^6-*p*-cymene)Os(OCH$_3$)(IPr)]OTf, which has been isolated as a brown solid in high yield. The isopropoxide counterpart is much less stable and rapidly leads to the hydride–acetone derivative [Os(η^6-*p*-cymene)OsH(κ^1–OC(CH$_3$)$_2$}(IPr)]OTf by means of a hydrogen *β*-elimination reaction.[16] In accordance with this, the *α*-alkylation of arylnitriles can be rationalized according to Scheme 1. Under the catalytic conditions, the hydroxo–alkoxide exchange should afford **2**, which should be the key species of the process. Thus, a *β*-hydrogen elimination reaction on its alkoxide group could give the hydride–aldehyde derivative **3**. The subsequent dissociation of the oxygen donor ligand should lead to the unsaturated monohydride **4**. Then the free aldehyde could undergo a Knoevenagel condensation[18] with the arylacetonitrile to give water and an *α*,*β*-unsaturated nitrile, which should insert into the Os–H bond of **4** to afford **5**. Thus, the addition of the O–H bond of a new alcohol molecule to the Os–C bond of **5** could finally yield the alkylation product and regenerate **2**.

Scheme 1. Proposed Mechanism for the Catalysis



The Knoevenagel condensation is catalyzed by the base. It implies the initial deprotonation of the methylene group of the nitrile and the subsequent nucleophilic attack of the generated α-cyano carbanion to the aldehyde carbon atom. The deprotonation appears to be a determining step of the overall process. Thus, it should be noted that electron-donating substituents at the para position of the aromatic ring of the nitrile slow down the reaction, whereas electron-donating substituents at the para position of the phenyl group of the benzyl alcohol, which should decrease the electrophilicity of the aldehyde, increase the alkylation rate. This is in contrast with that observed by Lin and Lau for the α-alkylation of arylacetonitriles with primary alcohols catalyzed by dialkylaminocyclopentadienylruthenium(II) complexes.[6] Ruthenium and iridiumhydride complexes have been demonstrated to catalyze the Knoevenagel condensation;[19] however, this is not the case of **4**. Although the latter and the aldehyde are generated by reaction of **1** with the alcohol, the alkylation does not occur in the absence of base.

The α-alkylation of methyl ketones can be rationalized in a similar manner with the particularity that the reduction of the α,β-unsaturated ketone, generated from the Knoevenagel condensation, should take place via a hydroxyallyl intermediate, as has been previously shown by us.[20] In this case, the nucleophilic attack of the enolate to the carbon atom of the aldehyde during the Knoevenagel condensation appears to have a significant contribution to the rate of the overall process. Thus, electron-donating substituents at the para position of the aromatic ring of benzyl alcohol slow down the reaction.

In conclusion, these results point out that osmium must be taken into account to develop the *borrowing hydrogen methodology*, since it can afford catalysts more efficient than those based on traditional metals, in particular for some reactions such as the α-alkylations of arylacetontriles and methyl ketones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and spectroscopy details for all the products. This information is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: maester@unizar.es (M. A. E.), yus@ua.es (M.Y.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Spanish MINECO [Projects CTQ2007-65218/BQU, CTQ2011-23459, CTQ2011-24165, and Consolider Ingenio 2010 (CSD2007-00006)], the DGA (E35), Generalitat Valenciana (PROMETEO/2009/039 and FEDER), and the European Social Fund (FSE) is acknowledged. Dedicated to Prof. Antonio Laguna on the occasion of his 65th birthday.

■ REFERENCES

(1) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753.

(2) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358.

(3) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *Tetrahedrom Lett.* **1981**, *22*, 4107.

(4) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023.

(5) Sawaguchi, T.; Obora, Y. *Chem. Lett.* **2011**, *40*, 1055.

(6) Cheung, H. W.; Li, J.; Zheng, W.; Zhou, Z.; Chiu, Y. H.; Lin, Z.; Lau, C. P. *Dalton Trans.* **2010**, *39*, 265.

(7) (a) Motokura, K.; Nishimura, D.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 5662. (b) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Chem. Eur, J.* **2006**, *12*, 8228.

(8) (a) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020. (b) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2002**, *43*, 7987. (c) Martínez, R.; Brand, G. J.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 3683. (d) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988. (e) Kuwahara, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2012**, *14*, 4703.

(9) (a) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72. (b) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819. (c) Morita, M.; Obora, Y.; Ishii, Y. *Chem. Comun.* **2007**, 2850.

(10) (a) Cho, C. S. *J. Mol. Catal. A: Chem.* **2005**, *240*, 55. (b) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913. (c) Yamada, Y. M. A.; Uozumi, Y. *Org. Lett.* **2006**, *8*, 1375.

(11) (a) Esteruelas, M. A.; Oro, L. A. *Adv. Organomet. Chem.* **2001**, *47*, 1. (b) Esteruelas, M. A.; López, A. M. *Organometallics* **2005**, *24*, 3584. (c) Esteruelas, M. A.; López, A. M.; Oliván, M. *Coord. Chem. Rev.* **2007**, *251*, 795. (d) Jia, G. *Coord. Chem. Rev.* **2007**, *251*, 2167.

(12) Although osmium has enabled oxidation catalysts, the danger of its oxides that are associated with high volatility has negatively influenced its general use.

(13) See, for example: (a) Barrio, P.; Esteruelas, M. A.; Oñate, E. *Organometallics* **2004**, *23*, 1340. (b) Batuecas, M.; Esteruelas, M. A.; García-Yebra, C.; Oñate, E. *Organometallics* **2010**, *29*, 2166. (c) Varela-Fernández, A.; García-Yebra, C.; Varela, J. A.; Esteruelas, M. A.; Saá, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 4278. (d) Baratta, W.; Barbato, C.; Magnolia, S.; Siega, K.; Rigo, P. *Chem.—Eur. J.* **2010**, *16*, 3201. (e) Baratta, W.; Benedetti, F.; Del Zotto, A.; Fanfoni, L.; Felluga, F.; Magnolia, S.; Putiganano, E.; Rigo, P. *Organometallics* **2010**, *29*, 3563.

(f) Baratta, W.; Bossi, G.; Putignano, E.; Rigo, P. *Chem.—Eur. J.* **2011**, *17*, 3474. (g) Esteruelas, M. A.; Honczeck, N.; Oliván, M.; Oñate, E.; Valencia, M. *Organometallics* **2011**, *30*, 2468. (h) Bertoli, M.; Choualeb, A.; Lough, A. L.; Moore, B.; Spasyuk, D.; Gusev, D. G. *Organometallics* **2011**, *30*, 3479. (i) Esteruelas, M. A.; García-Obregón, T.; Herrero, J.; Oliván, M. *Organometallics* **2011**, *30*, 6402. (j) Spasyuk, D.; Smith, S.; Gusev, D. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 2772.

(14) NHCs are versatile ligands that are receiving a great deal of attention in homogeneous catalysis. See, for example: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Corberán, R.; Mas-Marzá, E.; Peris, E. *Eur. J. Inorg. Chem.* **2009**, 1700. (c) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109*, 3677. (d) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.

(15) Castarlenas, R.; Esteruelas, M. A.; Oñate, E. *Organometallics* **2005**, *24*, 4343.

(16) Castarlenas, R.; Esteruelas, M. A.; Oñate, E. *Organometallics* **2008**, *27*, 3240.

(17) Buil, M. L.; Cadierno, V.; Esteruelas, M. A.; Gimeno, J.; Herrero, J.; Izquierdo, S.; Oñate, E. *Organometallics* **2012**, *31*, 6861.

(18) (a) Simon, C.; Constantieux, T.; Rodríguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (b) Sabitha, G.; Fatima, N.; Reddy, E. V.; Yadav, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1353.

(19) Lin, Y.; Zhu, X.; Xiang, M. *J. Organomet. Chem.* **1993**, *448*, 215.

(20) Esteruelas, M. A.; Hernández, Y. A.; López, A. M.; Oliván, M.; Oñate, E. *Organometallics* **2005**, *24*, 5989.