EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Brønsted Acid-Catalyzed Intramolecular α-Arylation of Ketones with Phenolic Nucleophiles via Oxy-Allyl Cation Intermediates

Authors: Yusuke Aota, Yuki Doko, Taichi Kano, and Keiji Maruoka

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000169

Link to VoR: http://dx.doi.org/10.1002/ejoc.202000169

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.202000169

WILEY-VCH

COMMUNICATION

Brønsted Acid-Catalyzed Intramolecular α-Arylation of Ketones with Phenolic Nucleophiles via Oxy-Allyl Cation Intermediates

Yusuke Aota,[a] Yuki Doko,[a] Taichi Kano*[a] and Keiji Maruoka*[a,b,c]

Abstract: Nucleophilic addition to the oxy-allyl cation intermediate has been emerged as a promising methodology for functionalization of the α-position of carbonyl compounds in an umpolung fashion. However, a structure of available carbon nucleophiles to trap the catalytically generated oxy-allyl cation has been limited to highly nucleophilic ones. Herein, we report the Brønsted acid-catalyzed α-arylation of ketones employing less explored phenolic nucleophiles as carbon nucleophiles in the oxy-allyl cation catalysis, affording ketones bearing an all carbon quaternary center at the α-position.

Arylation at the α-position of carbonyl compounds is one of the important transformations in synthetic chemistry since products are valuable building blocks and represent a common structure in natural products and pharmaceuticals.[1] Among them, carbonyl compounds having an all-carbon quaternary center at the α-position are quite attractive, but still difficult to access.[2] In order to prepare such motifs, a variety of methodologies have been developed to date.[3] Generally, α-arylation of carbonyl compounds mainly relies on the reaction between an electrophilic arylating agent and a nucleophilic enolate or its equivalent (Figure 1a).[4,5] On the other hand, α-arylation through nucleophilic addition of aromatic nucleophiles to an electrophilic α-carbon of carbonyl compounds has been less explored.[6]

Recently, a strategy based on nucleophilic addition to the oxy-allyl cation intermediate has been emerged as an alternative methodology for the functionalization of the α-position of ketones in an umpolung fashion.[7,8] The key oxy-allyl cation intermediate is a transient electrophilic species, which can be generated from the corresponding ketones bearing a leaving group at the α-position with the assistance of an acid or a base and can be captured with an appropriate nucleophile. Based on this strategy, in the presence of a stoichiometric amount of an acid or a base, a broad range of nucleophiles, including nitrogen-, oxygen-, sulfur- and carbon-based ones, can be utilized for α-functionalization of ketones.[8,9] However, applicable carbon nucleophiles to trap the catalytically generated oxy-allyl cation intermediates are limited to highly nucleophilic ones such as indoles and silyl enol ethers.[8i,10]

[a] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
E-mail: kano@kuchem.kyoto-u.ac.jp
http://kuchem.kyoto-u.ac.jp/yugo/.ac.jp
[b] Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto 606-8501, Japan
[c] School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China
E-mail: maruoka@kuchem.kyoto-u.ac.jp
http://www.pharm.kyoto-u.ac.jp/orgcat/index.html
Supporting information for this article is given via a link at the end of the document.

According to Mayr's nucleophilicity parameters (*N*), their *N* values range from 7.26 to 2.83 and 10.38 to 5.21 for substituted indoles and silyl enol ethers, respectively (Figure 1b).[11] Additionally, pyrrole (*N* = 4.63) and alkenyl- or alkynyl tetrafluoroborates have been employed as the carbon nucleophile in the oxy-allyl cation catalysis.[10b–d,10g] In contrast, development of catalytic α-functionalization with less nucleophilic carbon nucleophiles still remains a challenge. This limitation might be attributed to the low concentration of the oxy-allyl cation intermediate under catalytic conditions, and consequently, less reactive nucleophiles could not trap the transient oxy-allyl cation intermediate effectively. In this context, we have been interested in the possibility of using phenol derivatives (*N* = –1.18) as the carbon nucleophile in the oxy-allyl cation catalysis, to achieve the α-arylation of ketones. This methodology would provide an alternative approach for the

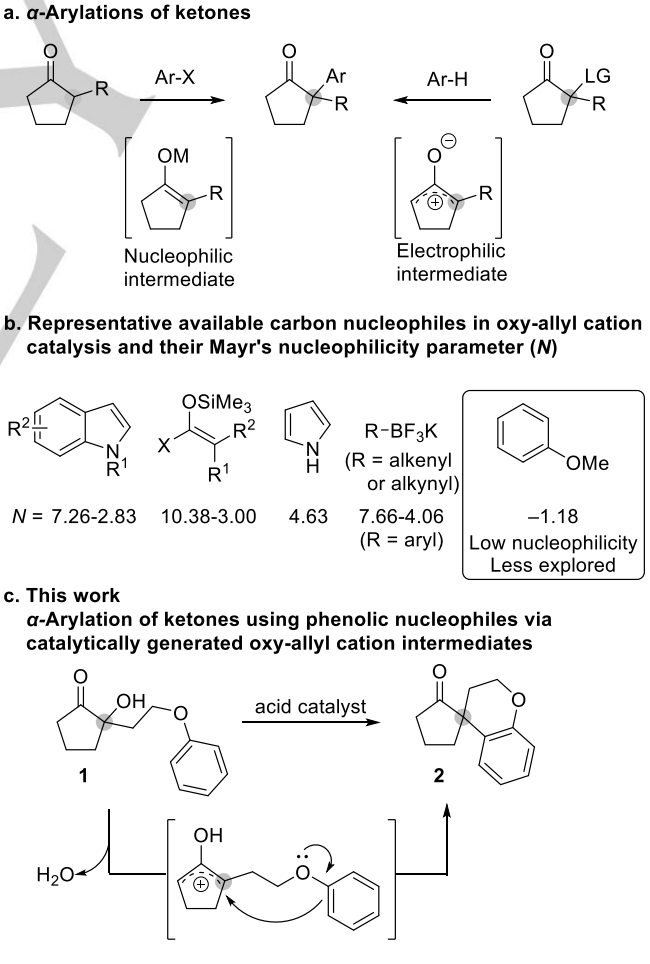
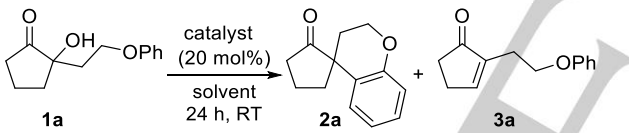


Figure 1. Strategies for α-arylation of ketones.

preparation of *α*-aryl ketones, which are important structural motifs in synthetic chemistry. Herein, we describe Brønsted acid-catalyzed intramolecular *α*-arylation of ketones with a tethered phenolic nucleophile (Figure 1c). The resulting products have a chroman skeleton, which is an important motif found in bioactive compounds, bearing an all-carbon quaternary stereogenic center.[12]

We first examined the intramolecular *α*-arylation of *α*-hydroxy cyclopentanone **1a**, bearing a tethered phenoxy group in the presence of 20 mol% of $TsOH·H_2O$ in various solvents at room temperature (Table 1). The reactions in toluene, CH_2Cl_2 or MeCN provided the desired spirocyclic ketone **2a** in low yield, along with the preferential formation of enone **3a** probably due to instability of the oxy-allyl cation intermediate in these solvents (entries 1–3). When DMSO, THF or EtOH was used as solvent, the desired **2a** was not obtained (entries 4–6). To our delight, with a fluorinated alcohol such as trifluoroethanol (CF_3CH_2OH), which is known to be an effective solvent in nucleophilic functionalization of the oxy-allyl cation intermediate, **2a** was formed exclusively (entry 7).[13,14] The conditions in entry 7 was applied to the reaction of the independently synthesized enone **3a** to investigate the possibility of the formation of **2a** from **3a**, and consequently, no reaction was observed. Use of less acidic CF_3CO_2H or $(PhO)_2PO_2H$ as catalyst in CF_3CH_2OH resulted in a significantly decreased yield (entries 8 and 9). Increasing the concentration (0.4 M) led to a similar yield with lower catalyst loading (10 mol%) (entry 10). Hexafluoroisopropanol ($(CF_3)_2CHOH$) was also found to be a suitable solvent for the present *α*-arylation (entry 11).

Table 1. Optimization of reaction conditions.[a]



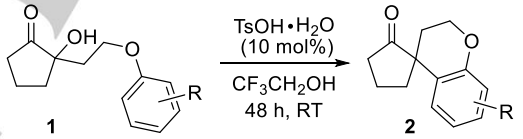
1a **2a** **3a**

Entry	Solvent	Catalyst	**2a** [%][b]	**3a** [%][b]
1	toluene	$TsOH·H_2O$	12	36
2	CH_2Cl_2	$TsOH·H_2O$	6	43
3	MeCN	$TsOH·H_2O$	15	71
4	DMSO	$TsOH·H_2O$	0	0
5	THF	$TsOH·H_2O$	0.	0.
6	EtOH	$TsOH·H_2O$	0	43
7	CF_3CH_2OH	$TsOH·H_2O$	98	1
8	CF_3CH_2OH	CF_3CO_2H	17	0
9	CF_3CH_2OH	$(PhO)_2PO_2H$	0	0
10[c]	CF_3CH_2OH	$TsOH·H_2O$	96	0
11[c]	$(CF_3)_2CHOH$	$TsOH·H_2O$	95	0

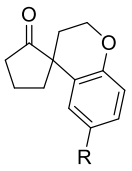
[a] Reactions were performed on a 0.1 mmol scale in 0.5 mL of solvent (0.2 M). [b] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Reaction was performed at 0.4 M in the presence of 10 mol% of $TsOH·H_2O$.

We next investigated the scope of *α*-hydroxy cyclopentanones having a series of phenolic nucleophiles (Table 2). Reactions of ketones bearing an electron-rich *para*-methylphenyl group or *para*-methoxyphenyl group afforded the corresponding products in high yields (**2b** and **2c**). While the introduction of an electron withdrawing group such as Br and CF_3 at the *para*-position led to low yield (46% and 11%, respectively) due to the undesired enone formation, use of TfOH as catalyst in $(CF_3)_2CHOH$ allowed the formation of the desired products in moderate to good yields (**2d** and **2e**). On the other hand, in the presence of TfOH, reactions of substrates bearing an ester or a sulfonamide group gave the corresponding enones preferentially, presumably because protonation of these groups by TfOH lowered the reactivity of the corresponding phenolic nucleophiles. In these cases, use of less acidic 4-NO_2-C_6H_4-SO_3H enabled the formation of the cyclized products in moderate to good yields (**2f** and **2g**). The present method was not compatible with phenolic nucleophile bearing a cyano group, probably due to its strong electron withdrawing nature and further deactivation by protonation (**2h**). The *meta*-substitution resulted in the formation of the corresponding products **2i**–**2l** in moderate to high yields. Remarkably, in these cases, the reaction proceeded at the sterically less hindered *ortho*-position, affording a single regioisomer. Incorporation of *ortho*-methy group had no detrimental effect on the reactivity, providing the desired product **2m** in 89% yield. Despite its steric hindrance, 2-naphthoxy group reacted at the more sterically hindered position exclusively (**2n**).[15] The practicability of the present method was demonstrated with a 5 mmol scale of reaction, giving 1.0 g of **2a** in 91% yield.

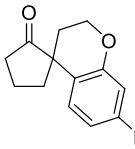
Table 2. Intramolecular *α*-Arylation of cyclopentanones bearing various phenolic nucleophiles.[a]



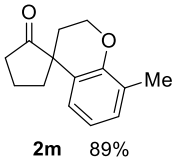
1 **2**



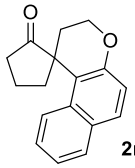
2a R = H 93% **2e** R = CF_3 55%[b,c]
2b R = Me 89% **2f** R = CO_2Et 62%[c,d]
2c R = OMe 94% **2g** R = NMe(Ts) 75%[c,d]
2d R = Br 87%[b,c] **2h** R = CN 0%



2i R = Me 90%
2j R = OMe 40%
2k R = F 92%[c]
2l R = Br 93%[b,c]



2m 89%



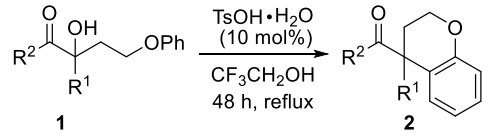
2n 87%

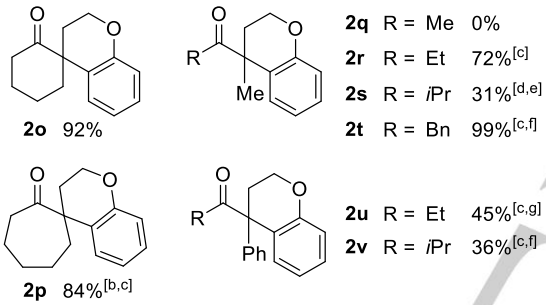
[a] Reactions were performed on a 0.2 mmol scale in 0.5 mL of solvent (0.4 M). [b] TfOH as catalyst. [c] $(CF_3)_2CHOH$ as solvent. [d] 4-NO_2-C_6H_4-SO_3H as catalyst.

We next turned our attention toward substrate scope of ketone moiety (Table 3). Cyclic *α*-hydroxy ketones having a larger ring size were well tolerated (**2o** and **2p**). Acyclic ketones were also suitable substrates for the present *α*-arylation. The effect of a

carbon substituent (R^2) at the carbonyl group on the reaction efficiency was investigated using *α*-hydroxy ketones bearing a methyl group at the *α*-position (R^1 = Me). Introduction of a methyl group on the carbonyl group (R^2 = Me) led to no product formation (**2q**). In contrast, replacement of the methyl group on the carbonyl carbon with ethyl group (R^2 = Et) resulted in the formation of the desired product **2r** in 72% yield. The yield of the reaction with isopropyl-substituted ketone was diminished presumably due to instability of the corresponding oxy-allyl cation intermediate by steric congestion (**2s**). Introduction of benzyl group significantly improved the yield, since the oxy-allyl cation intermediate can be stabilized by conjugation with the *π*-system (**2t**).[10b] On the other hand, reactions of **1u** or **1v** (R^1 = Ph), which has a phenyl group at the *α*-position, resulted in low to moderate yields (**2u** and **2v**).

Table 3. Substrate scope of ketones.[a]





[a] Reactions were performed on a 0.2 mmol scale in 0.5 mL of solvent (0.4 M). [b] Reaction was performed at rt in the presence of 10 mol% of TfOH. [c] $(CF_3)_2CHOH$ as solvent. [d] Use of 20 mol% of $TsOH•H_2O$. [e] Performed for 96 h. [f] Performed at 50 °C. [g] Performed at 40 °C.

The utility of this method was demonstrated through the transformation of the obtained arylation product **2a** (Figure 2). Baeyer−Villiger oxidation with *m*CPBA afforded spirocyclic lactone **4** having a tetrasubstituted carbon center at *δ*-position in 91% yield. A cyclopentane **5** with two adjacent tetrasubstituted carbon centers was obtained as a single diastereomer through a nucleophilic addition of allylmagnesium bromide to the carbonyl group of **2a**.[16] The ketone **2a** was readily converted to the corresponding enol triflate **6** in high yield by treating with Tf_2O in the presence of 2,6-di-*tert*-butylpyridine. The resulting **6** could be transformed to a cyclopentene **7** with a 2-bromoethyl group and an aryl group on the allylic position by BBr_3-mediated ring-opening reaction and the following introduction of trifluoromethanesulfonyl group to the resulting phenolic hydroxy group. Finally, hydrolysis of the enol triflate **7** mediated by a cobalt salt and triethylsilane under oxygen atmosphere led to formation of the corresponding cyclopentanone **8** bearing the all-carbon quaternary center at the carbonyl *α*-position.[17]

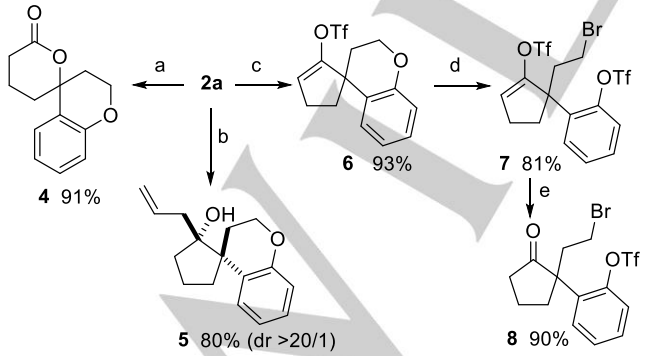
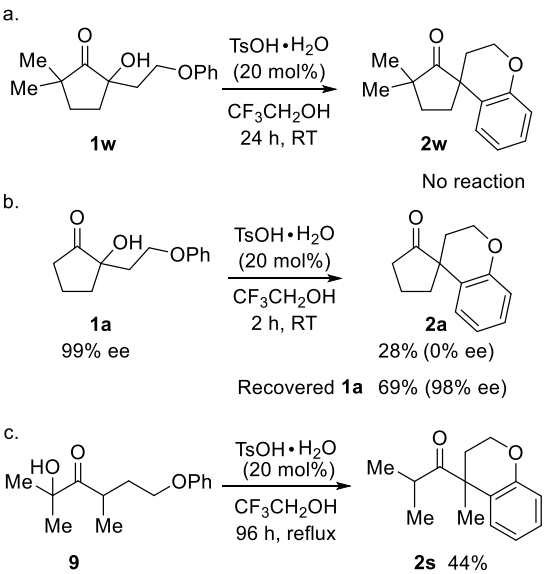


Figure 2. Derivatization of arylation product **2a**. [a]*m*CPBA, Li_2CO_3, $PhCH_3$. [b]allylmagnesium bromide, THF. [c]Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2. [d]BBr_3, CH_2Cl_2, then Tf_2O, pyridine, CH_2Cl_2. [e]$Co(acac)_2$, Et_3SiH, O_2, *i*PrOH.

To gain insight into the mechanism of the present *α*-arylation, we performed some reactions as shown in Scheme 1. The present *α*-arylation conditions were applied to the reaction of *α*-hydroxy ketone **1w**, which has two geminal methyl groups at *α*'-position, and no reaction was observed (Scheme 1a). This result indicates that the enolization of the *α*-hydroxy ketone would be necessary to generate the oxy-allyl cation intermediate. We then employed optically active **1a** (99% ee) and quenched the reaction after 2 h. The ketone **1a** was recovered in 69% yield with 98% ee along with the formation of racemic **2a** in 28% yield, suggesting that the stereochemical information of the *α*-position is lost during the reaction and the *α*-position of the ketone is planarized before the carbon-carbon bond forming step (Scheme 1b). Additionally, utilizing **9** as a substrate led to the formation of **2s**, which was obtained in the reaction with **1s** under the identical conditions (Scheme 1c). This result implies that the same intermediate would be generated from **9** and **1s** before the carbon-carbon bond forming step. These observations would support the presence of the proposed oxy-allyl cation intermediate as the key electrophilic species under the present conditions.[8f]



Scheme 1. Mechanistic investigation.

Based on the above mechanistic investigation, a plausible catalytic cycle for the present reaction is proposed in Figure 3. Enolization of the *α*-hydroxy ketone **1a** would be accelerated by the Brønsted acid catalyst (HX). Subsequently, protonation of the hydroxy group at the allylic position of the resulting enol would allow the formation of the intermediate **A**, followed by the generation of the key oxy-allyl cation intermediate **B** and water. Then, nucleophilic addition of the tethered phenolic nucleophile to the electrophilic *α*-position would afford the intermediate **C**. Finally, deprotonation by the counteranion and rearomatization would lead to the formation of the spirocyclic ketone **2a** and regeneration of the acid catalyst.

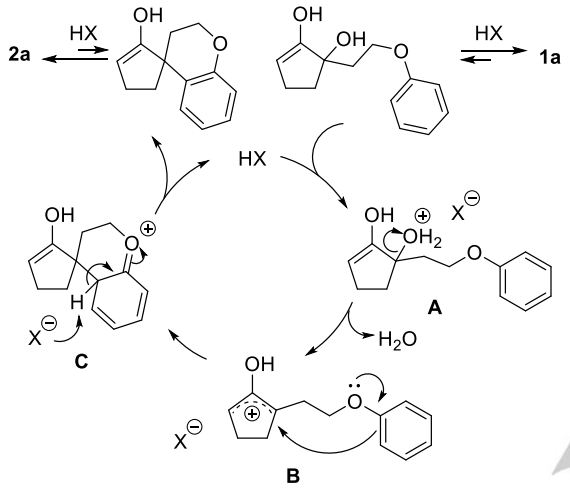


Figure 3. Proposed mechanism.

In summary, we have developed the Brønsted acid-catalyzed intramolecular *α*-arylation of ketones via the oxy-allyl cation intermediate using the tethered phenolic nucleophiles. This study has demonstrated that less nucleophilic phenols can be employed as the carbon nucleophiles for the functionalization of the catalytically generated oxy-allyl cation intermediate, expanding the utility of that intermediate in the catalytic *α*-functionalization of ketones.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP17H06450, JP26220803, and JP18H01975. Y.A. is grateful for Fellowships for Young Scientists from the Japan Society for the Promotion of Science (JSPS).

Keywords: umpolung • acid catalyst • arylation • quaternary stereocenters • ketones

[1] a) C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, *49*, 676; *Angew. Chem.* **2010**, *122*, 686; b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; c) C. Mazet, *Synlett* **2012**, *23*, 1999; d) H. K. Potukuchi, A. P. Spork, T. J. Donohoe, *Org. Biomol. Chem.*, **2015**, *13*, 4367; e) P. J. Moon, R. J. Lundgren, *Synlett* **2017**, *28*, 515; f) E. Barde, A. Guérinot, J. Cossy, *Synthesis* **2019**, *51*, 178; g) Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou, J.-S. Yu, *ACS Catal.* **2020**, *10*, 955.

[2] a) S. F. Martin, *Tetrahedron* **1980**, *36*, 419; b) K. Fuji, *Chem. Rev.* **1993**, *93* , 2037; c) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388; *Angew. Chem.* **1998**, *110*, 2029; d) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; *Angew. Chem.* **2001**, *113*, 4725; e) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; f) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943; g) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181; h) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740.

[3] a) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261; b) J. García-Fortanet, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 8108; *Angew. Chem.* **2008**, *120*, 8228; c) X. Liao, Z. Weng, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 195; d) A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900; e) Huang, N. Maulide, *J. Am. Chem. Soc.* **2011**, *133*, 8510; f) P. Li, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 6396; *Angew. Chem.* **2011**, *123*, 6520; g) X. Huang, M. Patil, C. Fares, W. Thiel, N. Maulide, *J. Am. Chem. Soc.* **2013**, *135*, 7312; h) T. Kano, Y. Hayashi, K. Maruoka, *J. Am. Chem. Soc.* **2013**, *135*, 7134; i) Z. Jia, E. Glvez, R. M. Sebastián, R. Pleixats, Á, Álvarez-Larena, E. Martin, A. Vallribera, A. Shafir, *Angew. Chem. Int. Ed.* **2014**, *53*, 11298; *Angew. Chem.* **2014**, *126*, 11480; j) X. Yang, F. D. Toste, *Chem. Sci.* **2016**, *7*, 2653; k) E. J. Alexy, H. Zhang, B. M. Stoltz, *J. Am. Chem. Soc.* **2018**, *140*, 10109; l) J. Li, A. Bauer, G. Di Mauro, N. Maulide, *Angew. Chem. Int. Ed.* **2019**, *58*, 9816; *Angew. Chem.* **2019**, *131*, 9921; m) P. Zheng, Y. Zhai, X. Zhao, T. XU, *Org. Lett.* **2019**, *21*, 393; n) H. Wu, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2019**, *141*, 11372; o) D. Ma, C.-B. Miao, J. Sun, *J. Am. Chem. Soc.* **2019**, *141*, 13783; p) C. I. Jette, I. Geibel, S. Bachman, M. Hayashi, S. Sakurai, H. Shimizu, J. B. Morgan, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2019**, *58*, 4297; *Angew. Chem.* **2019**, *131*, 4341; q) E. J. Alexy, T. J. Fulton, H. Zhang, B. M. Stoltz, *Chem. Sci.* **2019**, *10*, 5996.

[4] For selected examples of the *α*-arylation of carbonyl compounds via enolate or its equivalent, see: a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108; b) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382; c) J. Morgan, J. T. Pinhey, B. A. Rowe, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1005; d) G. I. Elliott, J. P. Konopelski, M. M. Olmstead, *Org. Lett.* **1999**, *1*, 1867; e) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; f) H. Deng, J. P. Konopelski, *Org. Lett.* **2001**, *3*, 3001; g) T. Ooi, R. Goto, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 10494; h) M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670; i) S. Kobbelgaard, M. Bella, K. A. Jørgensen, *J. Org. Chem.* **2006**, *71*, 4980; j) Y. K. Ramtohul, A. Chartrand, *Org. Lett.* **2007**, *9*, 1029; k) K. M. Bogle, D. J. Hirst, D. J. Dixon, *Org. Lett.* **2007**, *9*, 4901; l) J. Alemán, S. Cabrera, E. Maerten, J. Overgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5520; *Angew. Chem.* **2007**, *119*, 5616; m) J. Alemán, B. Richter, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2007**, *46*, 5515; *Angew. Chem.* **2007**, *119*, 5611; n) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260; o) J. S. Harvey, S. P. Simonovich, C. R. Jamison, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 13782; p) Z. Huang, Z. Liu, J. Zhou, *J. Am. Chem. Soc.* **2011**, *133*, 15882; q) S. Ge, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 16330; r) K. Mohanan, Y. Coquerel, J. Rodriguez, *Org. Lett.* **2012**, *14*, 4686; s) Q.-L. Xu, H. Gao, M. Yousufuddin, D. H. Ess, L. Kürti, *J. Am. Chem. Soc.* **2013**, *135*, 14048; t) F. Zhou, T. G. Driver, *Org. Lett.* **2014**, *16*, 2916; u) E. Picazo, S. M. Anthony, M. Giroud, A. Simon, M. A. Miller, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.* **2018**, *140*, 7605.

[5] For selected examples of *α*-arylation of carbonyl compounds through transition metal catalyzed cross-coupling reaction between alkyl electrophiles and organometallic nucleophiles, see: a) S.Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264; b) P. M. Lundin, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11027; c) J. Mao, F. Liu, M. Wang, L. Wu, B. Zheng, S. Liu, J. Zhong, Q. Bian, P. J. Walsh, *J. Am. Chem. Soc.* **2014**, *136*, 17662; d) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 5520;

e) M. Jin, L. Adak, M. Nakamura, *J. Am. Chem. Soc.* **2015**, *137*, 7128; f) F. Liu, J. Zhong, Y. Zhou, Z. Gao, P. J. Walsh, X. Wang, S. Ma, S. Hou, S. Liu, M. Wang, M. Wang, Q. Bian, *Chem. Eur. J.* **2018**, *24*, 2059; g) B. Li, T. Li, M. A. Aliyu, Z. H. Li, W. Tang, *Angew. Chem. Int. Ed.* **2019**, *58*, 11355; *Angew. Chem.* **2019**, *131*, 11477.

[6] For selected examples of the *α*-arylation of carbonyl compounds in an umpolung fashion, see: a) K. C. Nicolaou, R. Reingruber, D. Sarlah, S. Bräse, *J. Am. Chem. Soc.* **2009**, *131*, 2086; b) J. C. Conrad, J. Kong, B. N. Laforteza, D, W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640; c) J. M. Um, O. Gutierrez, F. Schoenebeck, K. N. Houk, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 6001; d) T. Miyoshi, T. Miyakawa, M. Ueda, O. Miyata, *Angew. Chem. Int. Ed.* **2011**, *50*, 928; *Angew. Chem.* **2011**, *123*, 958; e) N. Y. More, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 804; f) S. Maksymenko, K. N. Parida, G. K. Pathe, A. A. More, Y. B. Lipisa, A. M. Szpilman, *Org. Lett.* **2017**, *19*, 6312; g) D. Kaiser, A. de la Torre, S. Shaaban, N. Maulide, *Angew. Chem. Int. Ed.* **2017**, *56*, 5921; *Angew. Chem.* **2017**, *129*, 6015; h) N. Takeda, M. Furuishi, Y. Nishijima, E. Futaki, M. Ueda, T. Shinada, O. Miyata, *Org. Biomol. Chem.* **2018**, *16*, 8940; i) N. M. Rezayee, V. H. Lauridsen, L. Næsborg, T. V. Q. Nguyen, H. N. Tobiesen, K. A. Jørgensen, *Chem. Sci.* **2019**, *10*, 3586, j) C. Ciccolini, L. De Crescentini, F. Mantellini, S. Santeusanio, G. Favi, *Org. Lett.* **2019**, *21*, 4388.

[7] For reviews of the oxy-allyl cation intermediate and its synthetic applicaions, see: a) H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **1973**, *12*, 819; *Angew. Chem.* **1973**, *85*, 877; b) H. Takaya, S. Makino, Y. Hayakawa, R. Noyori, *J. Am. Chem. Soc.* **1978**, *100*, 1765; c) R. Noyori, *Acc. Chem. Res.* **1979**, *12*, 61; d) R. Noyori, Y. Hayakawa, *Org. React.* **1983**, *29*, 163; e) H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **1984**, *23*, 1; *Angew. Chem.* **1984**, *96*, 29; f) T. T. Tidwell, *Angew. Chem. Int. Ed.* **1984**, *23*, 20; *Angew. Chem.* **1984**, *96*, 16; g) J. Mann, *Tetrahedron* **1986**, *42*, 4611; h) M. Harmata, *Tetrahedron* **1997**, *53*, 6235; i) J. H. Rigby, F. C. Pigge, *Org. React.* **1997**, *51*, 351; j) M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595; k) M. Harmata, P. Rashatasakhon, *Tetrahedron* **2003**, *59*, 2371; l) I. V. Hartung, H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **2004**, *43*, 1934; *Angew. Chem.* **2004**, *116*, 1968; m) B. Niess, H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **2005**, *44*, 26; *Angew. Chem.* **2005**, *117*, 26; n) Y. Tamaru, *Eur. J. Org. Chem.* **2005**, 2647; o) J. Huang, R. P. Hsung, *Chemtracts* **2005**, *18*, 207; p) M. A. Battiste, P. M. Pelphrey, D. L. Wright, *Chem. Eur. J.* **2006**, *12*, 3438; q) M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297; r) M. Harmata, *Chem. Commun.* **2010**, *46*, 8886; s) M. Harmata, *Chem. Commun.* **2010**, *46*, 8904; t) D. A. Foley, A. R. Maguire, *Tetrahedron* **2010**, *66*, 1131; u) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812; v) H. Li, J. Wu, *Synthesis* **2014**, *47*, 22.

[8] For selected examples of the nucleophilic addition to the oxy-allyl cation intermediate using ketones bearing a leaving group at the *α*-position as the precursor, see: a) A. W. Fort, *J. Am. Chem. Soc.* **1962**, *84*, 2620; b) K. Freter, *Justus Liebigs Ann. Chem.* **1978**, 1357; c) B. Föhlisch, R. Joachimi, *Chem. Ber.*, **1987**, *120*, 1951; d) J, Leitich, I. Heise, *Eur. J. Org. Chem*.**2001**,27072; e) M. Harmata, C. Huang, P. Rooshenas, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 8696; *Angew. Chem.* **2008**, *120*, 8824; f) Q. Tang, X. Chen, B. Tiwari, Y. R. Chi, *Org. Lett.* **2012**, *14*, 1922; g) M. N. Vander Wal, A. K. Dilger, D. W. C. MacMillan, *Chem. Sci.* **2013**, *4*, 3075; h) J. Luo, H. Zhou, J. Hu, R. Wang, Q. Tang, *RSC Adv.* **2014**, *4*, 17370; i) C. Liu, E. Z. Oblak, M. N. Vander Wal, A. K. Dilger, D. K. Almstead, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 2134; j) B. Yang, X. Zhai, S. Feng, Z. Shao, *Org. Chem. Front.*, **2018**, *5*, 2794; k) B. Wang, Q. Zhang, J. Luo, Z. Gan, W. Jiang, Q. Tang, *Molecules* **2019**, *24*, 2187.

[9] Oxy-allyl cation can also be generated as an intermediate in Nazarov cyclization. For selected examples of the interrupted Nazarov cyclization, see: a) D. B. D. Santos, A. R. Banaag, M. A. Tius, *Org. Lett.* **2006**, *8*, 2579; b) F. Dhoro, T. E. Kristensen, V. Stockmann, G. P. A. Yap, M. A. Tius, *J. Am. Chem. Soc.* **2007**, *129*, 7256; c) A. K. Basak, M. A. Tius, *Org. Lett.* **2008**, *10*, 4073; d) M. Harmata, C. Huang, P. Rooshenas, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 8696; *Angew. Chem.* **2008**, *120*, 8824; e) V. M. Marx, T. S. Cameron, D. J. Burnell, *Tetrahedron Lett.* **2009**, *50*, 7213; f) T. N. Grant, C. J. Rieder, F. G. West, *Chem. Commun.* **2009**, 5676; g) V. M. Marx, D. J. Burnell, *Org. Lett.* **2009**, *11*, 1229; h) V. M. Marx, D. J. Burnell, *J. Am. Chem. Soc.* **2010**, *132*, 1685; i) Y.-K. Wu, R. McDonald, F. G. West, *Org. Lett.* **2011**, *13*, 3584; j) V. M. Marx, F. M. LeFort, D. J. Burnell, *Adv. Synth. Catal.* **2011**, *353*, 64; k) Y.-K. Wu, C. R. Dunbar, R. McDonald, M. J. Ferguson, F. G. West, *J. Am. Chem. Soc.* **2014**, *136*, 14903; l) R. William, S. Wang, A. Malick, X.-W. Liu, *Org. Lett.* **2016**, *18*, 4458; m) C. W. Williams, R. Shenje, S. France, *J. Org. Chem.* **2016**, *81*, 8253; n) R. Volpe, R. J. Lepage, J. M. White, E. H. Krenske, B. L. Flynn, *Chem. Sci.* **2018**, *9*, 4644; o) C.-S. Wang, J.-L. Wu, C. Li, L.-Z. Li, G.-J. Mei, F. Shi, *Adv. Synth. Catal.* **2018**, *360,* 846; p) S. Gelozia, Y. Kwon, R. McDonald, F. G. West, *Chem. Eur. J.* **2018**, *24*, 6052; q) A. V. Yadykova, V. Z. Shirinian, *Adv. Synth. Catal.* (DOI: 10.1002/adsc.201901001).

[10] For selected examples of the nucleophilic addition to the oxy-allyl cation intermediate using enol ethers bearing a hydroxy group as the precursor, see: a) C. E. Ayala, N. S. Dange, F. R. Fronczek, R. Kartika, *Angew. Chem. Int. Ed.*, **2015**, *54*, 4641; *Angew. Chem.*, **2015**, *127*, 4724; b) N. S. Dange, J. R. Stepherson, C. E. Ayala, F. R. Fronczek, R. Kartika, *Chem. Sci.*, **2015**, *6*, 6312, c) C. E. Ayala, N. S. Dange, J. R. Stepherson, J. L. Henry, F. R. Fronczek, R. Kartika, *Org. Lett.* **2016**, *18*, 1084; d) J. A. Malone, A. H. Cleveland, F. R. Fronczek, R. Kartika, *Org. Lett.* **2016**, *18*, 4408; e) J. R. Stepherson, F. R. Fronczek, R. Kartika, *Chem. Commun.* **2016**, *52*, 2300; f) J. R. Stepherson, C. E. Ayala, N. S. Dange, R. Kartika, *Synlett* **2016**, *27*, 320; g) T. N. Nguyen, K. Setthakarn, J. A. May, *Org. Lett.* **2019**, *21*, 7837; h) C. G. Bresnahan, K. A. Taylor-Edinbyrd, A. H. Cleveland, J. A. Malone, N. S. Dange, A. Milet, R. Kumar, R. Kartika, *J. Org. Chem.* **2019**, *84*, 11, 7166.

[11] a) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66; c) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209; d) T. Tokuyasu, H. Mayr, *Eur. J. Org. Chem.* **2004**, 2791; e) S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088; f) T. A. Nigst, M. Westermaier, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.* **2008**, 2369; g) H. Laub, H. Yamamoto, H. Mayr, *Org. Lett.* **2010**, *12*, 5206; h) G. Berionni, V. Morozova, M. Heininger, P. Mayer, P. Knochel, H. Mayr, *J. Am. Chem. Soc.* **2013**, *135*, 6317; i) A. I. Leonov, D. S. Timofeeva, A. R. Ofial, H. Mayr, *Synthesis* **2019**, *51*, 1157.

[12] a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939; b) K. C. Nicolaou, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G. Q. Cao, R. L. Affleck, J. E. Lillig, *J. Am. Chem. Soc.* **2000**, *122*, 9954; c) H. C. Shen, *Tetrahedron* **2009**, *65*, 3931; d) R. Pratap, V. J. Ram, *Chem. Rev.* **2014**, *114*, 10476.

[13] a) J. - P. Bégué, D. Bonnet - Delpon, B. Crousse, *Synlett* **2004**, 18; b) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, 2925; c) S. Khaksar, *J. Fluorine Chem.* **2015**, *172*, 51; d) I, Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088.

[14] The structure of **2a** was determined by single crystal X-ray diffraction (CCDC-1971506).

[15] The structure of **2n** was determined by single crystal X-ray diffraction (CCDC-1971507).

[16] The relative configuration of **5** was determined by single crystal X-ray diffraction after conversion to the corresponding 1-naphthylcarbamate (CCDC-1971510).

[17] a) X. Ma, S. B. Herzon, *J. Org. Chem.* **2016**, *81*, 8673; b) Á. Velasco-Rubio, E. J. Alexy, M. Yoritate, A. C. Wright, B. M. Stoltz, *Org. Lett.* **2019**, *21*, 8962.

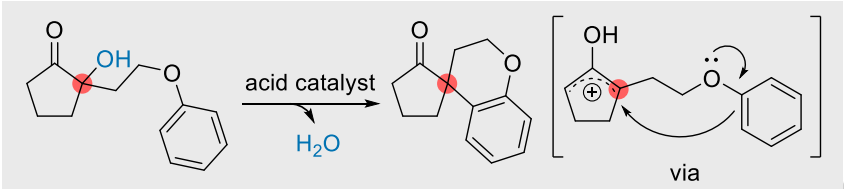
10.1002/ejoc.202000169

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Key Topic: Umpolung Arylation

COMMUNICATION



Yusuke Aota, Yuki Doko, Taichi Kano, Keiji Maruoka**

Page No. – Page No.

Brønsted Acid-Catalyzed Intramolecular *α*-Arylation of Ketones with Phenolic Nucleophiles via Oxy-Allyl Cation Intermediates

Catalytic *α*-arylation of ketones in an umpolung fashion was demonstrated through nucleophilic addition of phenol derivatives to the electrophilic oxy-allyl cation intermediates, allowing the formation of ketones bearing an all carbon quaternary center at the *α*-position.