COMMUNICATION

View Article Online
View Journal | View Issue Cite this: *RSC Adv.*, 2015, 5, 493Received 2nd November 2014
Accepted 17th November 2014

DOI: 10.1039/c4ra13647k

www.rsc.org/advances

Brønsted acid-catalyzed hydroarylation of activated olefins†

Ivana Fleischer^{*ab} and Jola Pospech^b

A mild, regiospecific Brønsted acid-catalyzed hydroarylation of activated olefins, capable of the formation of quinone methide-like intermediates, has been investigated. Various substituted 2- and 4-vinylphenols, 4-vinylaniline or 6-vinyl-naphthalen-2-ol were successfully implemented in a sequential protonation and Friedel–Crafts-type alkylation reaction of electron-rich arenes.

catalyst loading, excess of the nucleophile and inert reaction conditions were necessary.^{1c} Our strategy allowed for the use of 2- and 4-vinylphenols (–OH), 4-vinylaniline (–NH₂) and 6-vinyl-naphthalen-2-ol.

Introduction

A number of metal-catalyzed hydroarylations applying palladium,¹ cobalt,² rhodium,³ iridium,⁴ iron⁵ and other metal catalysts⁶ have been reported within the past 15 years. Besides that, it has been shown that Brønsted-acids are capable of promoting the coupling of electron-rich arenes with vinyl arenes⁷ and allylic and benzylic alcohols.⁸ However, all these protocols make use of strong acids and/or drastic reaction conditions thus limiting their applicability in conjunction with functionalized reactants.

We have recognized that hydroarylation of activated olefins, capable of forming a quinone methide-like intermediate,⁹ can be catalyzed by a number of mild Brønsted acids ($pK_a \sim 3$, see Table 1) simply by the generation of a stabilized carbocation and the following electrophilic substitution on electron-rich arenes (Scheme 1).¹⁰ The presence of hydroxyl or amino-group on the aryl attached to the double bond (the so-called activating group) enables application of relatively mild conditions for this kind of transformation. These substrates were applied in Pd-catalyzed hydroarylation by Sigman *et al.*, however high

Table 1 Hydroarylation of 2-vinylphenol: optimization^a

Acids:
Entry	Acid (x mol%)	T (°C)	Conv. ^b (%)	Yield ^{b,c} (%)
1	<i>rac</i> -A1 (8)	80	Quant.	94 (80)
2	<i>rac</i> -A1 (2)	80	82	76
3	<i>rac</i> -A1 (1)	80	59	58
4	<i>rac</i> -A1 (10)	25 ^d	16	16
5	A2 (2)	80	67	63
6	A3 (2)	80	38	38
7	A4 (2)	80	87	86
8	A5 (2)	80	58	42
9	A6 (2)	80	71	69
10	—	80	27	26
11	A2 (5)	60	37	33
12	A4 (5)	60	57	57
13	A5 (5)	60	49	46
14	A4 (5)	80	94	93 (88)

^aInstitut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, 93040 Regensburg, Germany. E-mail: ivana.fleischer@chemie.uni-regensburg.de

^bLeibniz Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

† Electronic supplementary information (ESI) available: Details of experimental procedures and physical properties of new compounds. CCDC 1016204. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra13647k

^a Reaction conditions: **1a** (60 mg, 0.50 mmol), **2a** (64 mg, 0.55 mmol), acid in DCM (1 mL), 16 h (with **1a** and **2a** stock solution). ^b Determined by GC with isooctane as internal standard. ^c Isolated yields are given in parentheses. ^d 40 hours.

Scheme 1 Proposed mechanism for the Brønsted acid-mediated hydroarylation of activated olefins.

Results and discussion

The initial tests of the reaction of 2-vinylphenol with indole were performed with racemic phosphoric acid **A1** at 80 °C (entry 1, Table 1). A quantitative conversion was obtained with 8 mol% of the acid. The desired product 2-(1-(1*H*-indol-3-yl)ethyl)phenol (**3aa**) was isolated in 80% yield. A decrease in yield is correlated with a decrease of the percentage of acid used, thus demonstrating its importance in this reaction. However, even with only 1 mol% of *rac*-**A1** a decent conversion of 58% to the desired product could be achieved (entry 3, Table 1) and, interestingly, 27% conversion was observed in the absence of the catalyst (entry 10, Table 1). Noteworthy, in previous protocols with different substrates, usually 10–20 mol% of strong acids (*p*TsOH,^{7c} H₂SO₄ or CF₃SO₃H^{8a}) have been used. Conversely, under the tested reaction conditions, strong acids did not lead to a full conversion of the starting materials (entries 5, 8 and 9, Table 1). Selected acids were also compared at lower temperature confirming that diphenyl hydrogen phosphate (**A4**) provides the best results (entries 11–13, Table 1). The most optimal outcome was achieved when 5 mol% of diphenyl hydrogen phosphate (**A4**) was used allowing to isolate **3aa** in 88% yield (entry 14, Table 1).

It is well known that protonated 2-vinylphenol can be described with its *ortho*-quinone methide resonance structure. This mesomeric form both stabilizes the positive charge and reinforces nucleophilic attack on the exocyclic carbon. Pathak and Sigman have shown that also 4-vinylphenol yields the desired hydroarylation product when reacted with indole (15 equiv.) under palladium-catalyzed reaction conditions, albeit in low yield (38%).^{1c} In the following, we have been interested if this mode of stabilization/reactivity can be translated to other structures able to form quinone methide-like intermediates applying Brønsted-acidic reaction conditions.

The results depicted in Table 2 support that the reaction is facilitated through the formation of an quinone methide intermediate that can be postulated for *ortho*- and *para*-vinylphenols (**3aa** and **3ba**) and anilines (**3ea**). The corresponding products were obtained in 64–88% yields. The presence of a

Table 2 Reactivity in dependence of the accessibility of the quinone methide intermediate^a

^a Reaction conditions: **1** (0.50 mmol), **2a** (64 mg, 0.55 mmol), **A4** (5.0 mol%), DCM (1 mL), 80 °C, 16 h. Isolated yields are given. ^b Reaction conditions: **A4** (10 mol%), DCE (1 mL), 100 °C, 16 h. GC-yield.

remote OH-group in a vinylnaphthalene derivative was also sufficient to promote the acid-catalyzed hydroarylation (**3da**). A substituent on the oxygen of the substrate had a disadvantageous influence on the reaction outcome, since higher temperature was necessary and several side-products were formed (**3ca**) impeding the isolation. Styrene derivatives lacking the possibility of mesomeric stabilization show no reactivity under the applied reaction conditions (**3fa** and **3ga**).

Next we investigated the scope of the Brønsted acid catalyzed hydroarylation reaction (Table 3). Therein we especially concentrated on altering functional groups on the electrophile **1**. In this respect, we could show that both functional groups attached to the phenol core (**3ka–na**) as well as substitution on the vinylic position (**3ha**, **3ia** and **3ja**) were well tolerated. To our surprise, sterically encumbered 2-(prop-1-en-2-yl)phenol **1h** proved to be an excellent substrate, assumingly due to superior stabilization of the α -carbenium species. The corresponding product **3ha** was isolated in 97% yield. Internal alkenes could also be successfully hydroarylated under Brønsted-acidic reaction conditions. 2-(buta-1,3-dien-1-yl)phenol reacted with indole under the formation of 2-(1-(1*H*-indol-3-yl)but-2-en-1-yl)phenol (**3ia**) in a combined yield of 67%. The *E/Z* stereoisomers (*E/Z* = 81 : 19) of **3ia** could be separated by column chromatography. Likewise, 2-(prop-1-en-1-yl)phenol resulted in the formation of 2-(1-(1*H*-indol-3-yl)propyl)phenol (**3ja**) in 90% isolated yield, albeit under more forcing conditions. Noteworthy, no

Table 3 Hydroarylation of alkenes with indole^a

hydroarylation activity was evident starting from 2-allylphenol underlying the importance of the accessibility of a quinone methide intermediate.

Table 4 Hydroarylation of 2-vinylphenol with indole derivatives^a Table 5 Hydroarylation of selected alkenes with 1,3,5-trimethoxybenzene **5**^a

Next, we investigated the scope of nucleophiles. Besides the excellent yields and expedient equimolar substrate ratios, in contrast to the Pd-catalyzed approach, the Brønsted-acid catalyzed hydroarylation tolerates halide substituents on the arene moiety (Table 4). 2-(1-(5-halo-1*H*-indol-3-yl)ethyl)phenol derivatives **3ab–3ad** were obtained in moderate yields of 52–63%. 1-Methyl indole was converted to the corresponding product **3ae** in 80% yield. In addition, two 2-substituted derivatives of indole were tested and the reaction provided the products **3af** and **3ag** in good yields. Unfortunately, 3-methyl indole furnished a mixture of the desired and oxidized compound and pyrrole led to a low conversion of a complex mixture.

Furthermore, we could demonstrate that the scope of the Brønsted-acid catalyzed hydroarylation can be further translated to common electron rich arenes, such as 1,3,5-trimethoxybenzene **5** (Table 5). It is noteworthy to mention that in this case an excess of the arene (2 equivalents) is required to obtain optimal results. Thus, 4-(1-(2,4,6-trimethoxyphenyl)ethyl)phenol (**6ba**) was isolated in 91% on 5 mmol scale.

Conclusions

In summary, we could demonstrate that the hydroarylation of activated olefins can be conveniently achieved by Brønsted-acid catalysis in the absence of transition-metal catalysts. The reaction follows a simple mechanism based on the formation of a stabilized carbocation, which serves as an electrophile in the Friedel-Crafts alkylation. The developed methodology does neither require the application of inert reaction conditions nor protection of the NH group of the indole. The hydroarylation products are obtained in moderate to excellent yields by applying a nearly equimolar substrate ratio. Compared to existing protocol, we extended the scope of the reaction to 4-vinylanilines and 6-vinylnaphthalene-2-ol and 5-halo indoles.

Our future endeavor encompasses the development of a stereoselective variant of the presented protocol by means of asymmetric Brønsted-acid catalysis.^{11–13}

Acknowledgements

We are grateful to the Leibniz Institute of Catalysis, Prof. Dr Matthias Beller and Fonds der Chemischen Industrie (Liebig Fellowship for I.F.) for the financial support. We thank the analytical departments, workshops and glassblowers of the Leibniz Institute of Catalysis and University of Regensburg for their support; and Dr A. Spannenberg for crystallographic analysis.

Notes and references

- For selected examples, see: (a) D. Drago and P. S. Pregosin, *Organometallics*, 2002, **21**, 1208–1215; (b) C. Liu and R. A. Widenhoefer, *Chem.-Eur. J.*, 2006, **12**, 2371–2382; (c) T. P. Pathak and M. S. Sigman, *Org. Lett.*, 2011, **13**, 2774–2777; (d) S. M. Podhajsky, Y. Iwai, A. Cook-Sneathen and M. S. Sigman, *Tetrahedron*, 2011, **67**, 4435–4441.
- For selected examples, see: (a) P.-S. Lee and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 1240–1244; (b) Z. Ding and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 8574–8578; (c) Z. Yang, H. Yu and Y. Fu, *Chem.-Eur. J.*, 2013, **19**, 12093–12103.
- (a) M. Beller, O. R. Thiel and H. Trauthwein, *Synlett*, 1999, 243–245; (b) R. Jana and J. A. Tunge, *Org. Lett.*, 2009, **11**, 971–974; (c) G. C. Tsui, F. Menard and M. Lautens, *Org. Lett.*, 2010, **12**, 2456–2459.
- (a) G. Bhalla, J. Oxgaard, W. A. Goddard and R. A. Periana, *Organometallics*, 2005, **24**, 3229–3232; (b) C. S. Sevov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 2116–2119.
- (a) J. Kischel, I. Jovel, K. Mertins, A. Zapf and M. Beller, *Org. Lett.*, 2005, **8**, 19–22; (b) S. Halder and S. Koner, *J. Org. Chem.*, 2010, **75**, 6005–6008.
- For selected examples, see: (a) Y. Uchamaru, *Chem. Commun.*, 1999, 1133–1134; (b) M. Rueping, B. J. Nachtsheim and T. Scheidt, *Org. Lett.*, 2006, **8**, 3717–3719; (c) Z. Zhang, X. Wang and R. A. Widenhoefer, *Chem. Commun.*, 2006, 3717–3719; (d) M. Rueping, B. J. Nachtsheim and W. Ieawsuwan, *Adv. Synth. Catal.*, 2006, **348**, 1033–1037; (e) M.-Z. Wang, M.-K. Wong and C.-M. Che, *Chem.-Eur. J.*, 2008, **14**, 8353–8364; (f) T. Mukai, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 6410–6413; (g) Y. Nakao, N. Kashiwara, K. S. Kanyiva and T. Hiyama, *Angew. Chem., Int. Ed.*, 2010, **49**, 4451–4454; (h) W.-C. Shih, W.-C. Chen, Y.-C. Lai, M.-S. Yu, J.-J. Ho, G. P. A. Yap and T.-G. Ong, *Org. Lett.*, 2012, **14**, 2046–2049.
- (a) A. E. Cherian, G. J. Domski, J. M. Rose, E. B. Lobkovsky and G. W. Coates, *Org. Lett.*, 2005, **7**, 5135–5137; (b) X. Zhao, Z. Yu, T. Xu, P. Wu and H. Yu, *Org. Lett.*, 2007, **9**, 5263–5266; (c) T. P. Pathak, J. G. Osiak, R. M. Vaden, B. E. Welm and M. S. Sigman, *Tetrahedron*, 2012, **68**, 5203–5208.
- (a) J. Le Bras and J. Muzart, *Tetrahedron*, 2007, **63**, 7942–7948; (b) M. Barbero, S. Cadamuro, S. Dughera, M. Rucci, G. Spano and P. Venturello, *Tetrahedron*, 2014, **70**, 1818–1826.
- (a) For review, see: T. P. Pathak and M. S. Sigman, *J. Org. Chem.*, 2011, **76**, 9210–9215; (b) For recent examples, see: J. C. Green, E. R. Brown and T. R. R. Pettus, *Org. Lett.*, 2012, **14**, 2929–2931; (c) M.-W. Chen, L.-L. Cao, Z.-S. Ye, G.-F. Jiang and Y.-G. Zhou, *Chem. Commun.*, 2013, **49**, 1660–1662; (d) V. A. Osyanin, D. V. Osipov and Y. N. Klimochkin, *J. Org. Chem.*, 2013, **78**, 5505–5520; (e) T. H. Jepsen, S. B. Thomas, Y. Lin, C. I. Stathakis, I. de Miguel and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2014, **53**, 6747–6751; (f) A. K. Shaikh and G. Varvounis, *Org. Lett.*, 2014, **16**, 1478–1481.
- M. Rueping, B. J. Nachtsheim and B. J. Beilstein, *J. Org. Chem.*, 2010, **6**, 6.
- For preliminary tests, see ESI.†
- For reviews on asymmetric Brønsted acid catalysis, see: (a) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744–5758; (b) D. Kampen, C. M. Reisinger and B. List, in *Asymmetric Organocatalysis*, ed. B. List, 2009, Springer Verlag, pp. 395–456; (c) M. Terada, *Synthesis*, 2010, 1929–1982; (d) A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2010, **8**, 5262–5276.
- Appeared during the preparation of the manuscript: O. El-Sepelgy, S. Haseloff, S. K. Alamsetti and C. Schneider, *Angew. Chem., Int. Ed.*, 2014, **53**, 7923.