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Synthesis of Furoquinolines by a One-Pot Multicomponent Cascade Reaction Catalyzed by Platinum Complexes

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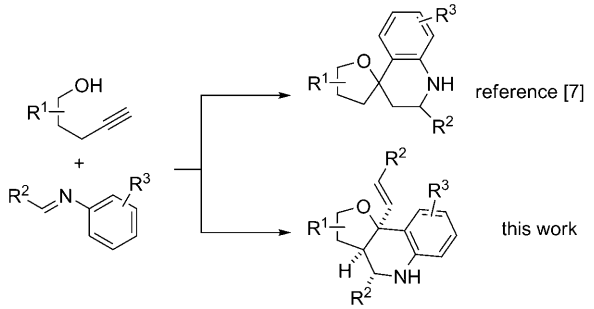
Tetrahydroquinolines have been found as a key structural unit in many bioactive natural products and pharmaceuticals.[1] In particular, furoquinoline derivatives are alkaloids mainly isolated from *Rutaceae* and *Solanaceae* plant species.[2] Owing to the relevant biological properties of both natural and synthetic analogues of these molecules,[3] which include antitumoral, antimicrobial, antibacterial, insecticide, analgesic, antipyretic, antiplatelet, and cytotoxic activities, the isolation and synthesis of new furoquinoline derivatives is an active and rewarding research area.[4] In this connection, the Povarov reaction is a powerful transformation that offers an easy entry to the furo[3,2-*c*]quinoline skeleton through a formal [4+2] cycloaddition between *N*-arylaldimines (as diene) and 2,3-dihydrofuran (as dienophile).[5] One of the main limitations of this reaction stems from the enol ether counterpart, since very few functionalized 2,3-dihydrofuran derivatives are available. In fact, the great majority of the furo[3,2-*c*]quinoline derivatives synthesized by this strategy are derived from the commercially available 2,3-dihydrofuran and basically no effort has been directed to the synthesis and study of the biological activity of furo[3,2-*c*]quinoline derivatives substituted at the furan ring. In this context, we thought that an easy entry to this kind of compounds could be a Povarov reaction[6] in which a functionalized furan was generated in situ from an alkynol derivative by a cycloisomerization reaction. Thus, we have recently reported a new synthesis of spirofuranquinoline derivatives by reaction of in situ generated *N*-arylaldimines and exocyclic enol ethers in a process in which a platinum complex and a Brønsted acid are used as catalysts (Scheme 1).[7] Further studies in this field led us to discover an unprecedented platinum-catalyzed three-component coupling reaction that allows the easy and diastereoselective synthesis of functionalized furoquinoline derivatives (Scheme 1),[8] and details of this process are given herein.



Scheme 1. Two different quinoline derivatives obtained from alkynols and *N*-arylaldimines.

As previously reported,[7] cationic platinum complexes were appropriate catalysts for the in situ formation of enol ethers by intramolecular hydroalkoxylation reactions. In that work the cationic platinum catalyst was formed from [(cod)$PtMe_2$] (cod = 1,5-cyclooctadiene) by treatment with a protic acid. Another possibility for the in situ generation of the cationic platinum complex is the treatment of [(cod)$PtCl_2$] with a silver salt under nonacidic conditions.

Accordingly, in an initial experiment we treated pentynol derivative **1a** with two equivalents of the imine **2a** in the presence of a cationic platinum complex generated in situ by mixing 5 mol% of [(cod)$PtCl_2$] and 10 mol% of $AgSbF_6$. This reaction led to a 3:1 mixture of the spirofuranquinoline derivative **3a** and the furo[3,2-*c*]quinoline **4a** (Table 1, entry 1). Bearing in mind our previous results,[7] the formation of compound **3a**, as a mixture of two diastereoisomers, could be considered as expected. Much more surprising was the isolation of the styryl-substituted furoquinoline **4a**. The formation of this compound supposes the coupling of three components, a unit of the alkynol **1a** and two units of the imine **2a**, in a process in which a molecule of 4-methoxyaniline is delivered. Moreover, furoquinoline **4a** was formed as

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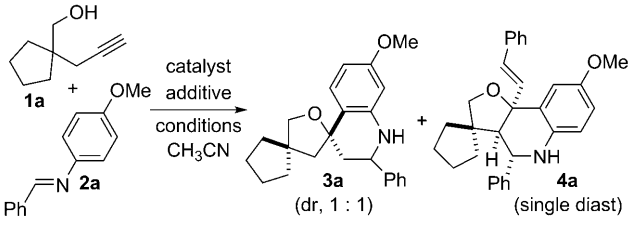
Table 1. Platinum-catalyzed reaction of alkynol **1a** and imine **2a** under different conditions.



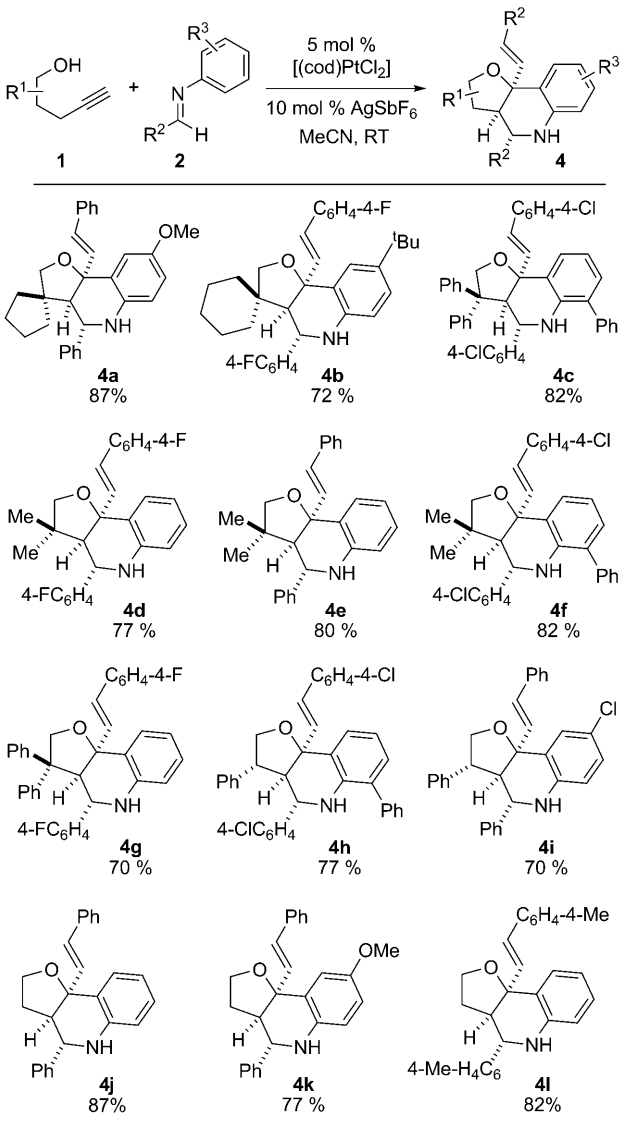
catalyst: 5 mol % $[(cod)PtCl_2]$, 10 mol % $AgSbF_6$

Entry	Equiv **2a**	Additive	Conditions	Ratio **3a**:**4a**[a]
1	2	none	standard[b]	3:1
2	2	HBF_4 (1 equiv)[c]	standard[b]	>20:1
3	4	none	standard[b]	1:2
4	4	none	slow addition[d]	1:>20
5	2	none	slow addition[d]	1:1

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] All reagents mixed at room temperature and the reaction mixture was stirred for 24 h. [c] Reagents mixed at −30 °C. [d] Alkynol **1a** slowly added to a solution of imine **2a** and the catalyst over a period of 7 h at room temperature. The reaction mixture was stirred for an additional 17 h.

a single diastereoisomer and remarkably, a quaternary stereocenter is generated. All these interesting structural features led us to consider the possibility of steering the reaction toward the formation of the vinyl-substituted furoquinoline **4a**. Thus, we tried the reaction under different conditions. We observed that the addition of one equivalent of the protic acid HBF_4 led to the exclusive formation of the spirofuranquinoline **3a** (Table 1, entry 2). In contrast, the amount of compound **3a** was decreased by the addition of an excess (4 equiv) of the starting imine **2a** (Table 1, entry 3). In particular, formation of compound **3a** was practically suppressed by the slow addition, over a period of 7 h, of the alkynol **1a** to a solution of the imine **2a** and the catalyst (Table 1, entry 4). However, using the slow addition conditions but reducing the amount of imine **2a** to two equivalents, led to a 1:1 mixture of **3a** and **4a** (Table 1, entry 5). Thus, we have suitable conditions to direct the reaction to the formation of the spirofuranquinoline **3a** (by adding a protic acid) or to the vinyl-substituted furoquinoline **4a** (by using a fourfold excess of the starting imine **2a** under slow addition conditions).

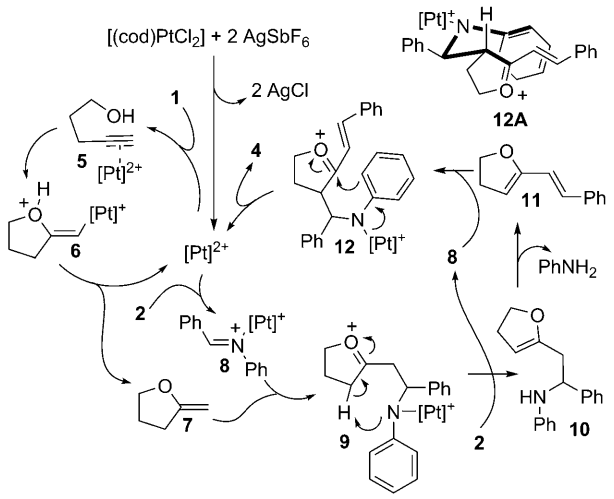
As previously mentioned, the structure of the vinyl-substituted furoquinoline **4** is very attractive and thus the substrate generality was examined under the optimized conditions. Various kinds of alkynols **1** and imines **2** were tested, and, as shown in Scheme 2, several vinyl-substituted furoquinoines **4** were synthesized and isolated in high yield and as single diastereoisomers in all cases attempted. Structural assignments of these new compounds were based on a series of NMR studies. Additionally, the structure of compound **4i** was confirmed by single-crystal X-ray diffraction analysis.[9] Those products containing fluorine atoms in their structure (**4b,d,g**) may prove to be particularly interesting, and the chlorine-substituted products **4c,f,h,i** could be interesting



Scheme 2. Furoquinolines **4** obtained by a catalytic three-component coupling reaction.

for further functionalization by well-established carbon–carbon couplings. The furoquinolines **4h,i** are also remarkable as they are derived from a chiral alkynol derivative. In these cases, we only observed the formation of a single diastereoisomer corresponding to those structures shown in Scheme 2. These results indicate that the substrate-controlled synthesis of enantiomerically pure furoquinoline derivatives **4** is possible.

A catalytic mechanism that explains the formation of furoquinolines **4** is shown in Scheme 3 (for simplicity substituents on the alkynol derivative **1** and the imine **2** are not considered). In this reaction, we suppose the formation of a reactive cationic platinum complex from $[(cod)PtCl_2]$ by reaction with $AgSbF_6$.[10] The reaction is initiated by coordination of the metallic complex to the triple bond of the starting alkynol **1** to form intermediate **5**. Intramolecular addition of the hydroxy group to the internal carbon of the



Scheme 3. Mechanism of formation of furoquinolines **4**.

triple bond generates **6**. Protodemetallation of the latter affords the enol ether **7** and releases the catalytic species.[11] Once enol ether **7** is formed, it enters the second catalytic cycle. Thus, the coordination of the nitrogen atom of the imine **2** to the platinum catalyst forms **8** and favors the addition of the enol ether **7** to give the intermediate **9** through a Mannich-type process.[12] Further reaction of the basic nitrogen atom with one of the acidic protons in the α-position to the oxonium group leads to the amine derivative **10**. An elimination of aniline in **10** gives the diene intermediate **11** which reacts with the previously formed imine complex **8** through a typical Povarov process to furnish the intermediate **12**.[13] Intramolecular nucleophilic addition of the electron-rich aromatic ring to the oxonium ion, followed by rearomatization and protodemetallation leads to the final product **4** closing the second catalytic cycle. To explain the stereochemistry observed in products **4** we suppose that the cyclization step in **12** occurs through a chairlike conformation in which the phenyl group occupies an equatorial position (see **12A** in Scheme 3; bold bonds were drawn to facilitate the visualization of the chairlike conformation).

Formation of the spirofuranquinoline **3a** under acidic conditions (see Table 1, entry 2), is easily understood by a mechanism analogous to that discussed in our previous work.[7] In a similar way, under neutral conditions, formation of the spirofuranquinoline **3a** could be explained by intramolecular nucleophilic addition of the aromatic ring to the oxonium ion in **9**. When an excess of imine **2** is used, and in particular under the slow addition conditions previously described, the concentration of imine **2** in the reaction media is high and we suppose that the ligand-exchange reaction in **9** to form **8** and the product **10** is favored. Thus, under the slow addition conditions, the intramolecular protonation in **9** seems to be more favored than the intramolecular nucleophilic addition of the aromatic ring to the oxonium ion.

In summary, we have developed a new platinum-catalyzed reaction for the diasteresoselective construction of furo[3,2-*c*]quinoline derivatives. The reaction is very straightforward, the starting materials are simple, and the products obtained cannot be easily synthesized by other methods. The new process supposes a one-pot three-component coupling reaction between a unit of an alkynol derivative and two units of an *N*-arylaldimine. Formally, the reaction could be considered a Povarov reaction in which the enol ether counterpart is generated in situ. This strategy allows the functionalization of the furan ring and leads to diastereomerically pure furoquinoline derivatives, thereby surpassing some of the limitations of the conventional Povarov reaction. Moreover, the presence of a vinyl moiety in the final products would allow further functionalization. The easy generation of molecular diversity coupled with the importance of furoquinoline derivatives in medicinal chemistry makes the reaction described herein an appropriate alternative for the synthesis of potentially bioactive compounds.

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Keywords: cyclization · domino reactions · homogeneous catalysis · platinum · quinolines

[1] See, for example: a) K. Schiemann, S. Anzali, H. Drosdat, U. Emde, D. Finsinger, J. Gleitz, B. Hock, H. Reubold, F. Zenke (Merck Patent GMBH, PCT Int. Appl.), WO 2005063735, **2005**; [*Chem. Abstr.* **2005**, *143*, 133291]; b) M. Nyerges, *Heterocycles* **2004**, *63*, 1685; c) K. Hanada, K. Furuya, K. Inoguchi, M. Miyakawa, N. Nagata (Kaken Pharma Co Ltd, PCT Int. Appl.), WO 01027086, **2001**,; [*Chem. Abstr.* **2001**, *134*, 295752]; d) M. Anzini, A. Cappelli, S. Vomero, G. Giorgi, T. Langer, M. Hamon, N. Merahi, B. M. Emerit, A. Cagnotto, M. Skorupska, T. Mennini, J. C. Pinto, *J. Med. Chem.* **1995**, *38*, 2692; e) D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck, D. Jasserand, *J. Med. Chem.* **1995**, *38*, 669; f) R. W. Carling, P. D. Leeson, A. M. Moseley, J. D. Smith, K. Saywell, M. D. Trickelbank, J. A. Kemp, G. R. Marshall, A. C. Foster, S. Grimwood, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65; g) A. Nakagawa, Y. Iwai, H. Hashimoto, N. Miyazaki, R. Oiwa, Y. Takahashi, A. Hirano, N. Shibukawa, Y. Kojima, S. Omura, *J. Antibiot.* **1981**, *34*, 1408.

[2] a) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 627; b) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 650; c) J. P. Michael, *Nat. Prod. Rep.* **2003**, *20*, 476; d) J. P. Michael, *Nat. Prod. Rep.* **2002**, *19*, 742; e) M. F. Grundon in *The Alkaloids, Vol. 32* (Ed.: A. Brossi), Academic Press, New York, **1988**, p. 341.

[3] See, for example: a) M. Z. Hoemann, R. L. Xie, R. F. Rossi, S. Meyer, A. Sidhu, G. D. Cuny, J. R. Hauske, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 129; b) A. Chilin, C. Marzano, A. Guiotto, F. Bacchichetti, F. Carlassare, F. Bordin, *J. Med. Chem.* **2002**, *45*, 1146; c) L. K. Basco, S. Mitaku, A.-L. Skaltsounis, N. Ravelomanantsoa, F. Tillequin, M. Koch, J. Le Bras, *Antimicrob. Agents Chemother.* **1994**, *38*, 1169, and references therein. See also references [1d] and [2].

[4] For leading recent references, see: a) Z. Zhang, Q. Zhang, S. Sun, T. Xiong, Q. Liu, *Angew. Chem.* **2007**, *119*, 1756; *Angew. Chem. Int. Ed.* **2007**, *46*, 1726; b) T. Godet, C. Vaxelaire, C. Michel, A. Milet, P. Belmont, *Chem. Eur. J.* **2007**, *13*, 5632; c) A. Fayol J. Zhu, *Angew.*

Chem. **2002**, *114*, 3785; *Angew. Chem. Int. Ed.* **2002**, *41*, 3633. See also reference [5].

[5] For selected examples, see: a) S. Vellaisamy, C. Avendaño, J. C. Menéndez, *Synlett* **2007**, 1079–1082; b) Z. Zhou, F. Xu, X. Han, J. Zhou, Q. Shen, *Eur. J. Org. Chem.* **2007**, 5265; c) K. Nagaiah, D. Sreenu, R. S. Rao, G. Vashishta, J. S. Yadav, *Tetrahedron Lett.* **2006**, *47*, 4409; d) R. Sridhar, P. T. Perumal, *Can. J. Chem.* **2006**, *84*, 464; e) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070; f) K. V. N. S. Srinivas, B. Das, *Synlett* **2004**, 1715; g) R. S. Kumar, R. Nagarajan, S. Chitra, P. T. Perumal, *Tetrahedron* **2001**, *57*, 3419; h) G. Sundararajan, N. Prabagaran, B. Varghese, *Org. Lett.* **2001**, *3*, 1973; i) B. Crousse, J. P. Bégué, D. Bonnet-Delpon, *J. Org. Chem.* **2000**, *65*, 5009; j) S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, *118*, 8977.

[6] L. S. Povarov, *Russ. Chem. Rev.* **1967**, *36*, 656.

[7] J. Barluenga, A. Mendoza, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2008**, *120*, 7152; *Angew. Chem. Int. Ed.* **2008**, *47*, 7044.

[8] For some recent reviews on different uses of platinum catalysts, see: a) A. R. Chianese, S. J. Lee, M. R. Gagné, *Angew. Chem.* **2007**, *119*, 4118–4136; *Angew. Chem. Int. Ed.* **2007**, *46*, 4042–4059; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) C. Liu, F. Bender, X. Han, R. A. Widenhoefer, *Chem. Commun.* **2007**, 3607–3618; d) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; e) L. Añorbe, G. Domínguez, J. Pérez-Castells, *Chem. Eur. J.* **2004**, *10*, 4938–4943; f) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431–436.

[9] CCDC-689851 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[10] Neither the platinum complex nor the silver salt are appropriate catalysts in this reaction and the mixture of both is required.

[11] Recent hydroalkoxylation reactions catalyzed by platinum complexes: a) J. Barluenga, A. Fernández, A. Satrústegui, A. Diéguez, F. Rodríguez, F. J. Fañanás, *Chem. Eur. J.* **2008**, *14*, 4153–4156; b) A. Diéguez-Vázquez, C. C. Tzschucke, W. Y. Lam, S. V. Ley, *Angew. Chem.* **2008**, *120*, 216–219; *Angew. Chem. Int. Ed.* **2008**, *47*, 209–212; c) I. Nakamura, C. S. Chan, T. Araki, M. Terada, Y. Yamamoto, *Org. Lett.* **2008**, *10*, 309–312; d) J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2006**, *118*, 2145–2147; *Angew. Chem. Int. Ed.* **2006**, *45*, 2091–2093; e) B. Liu, J. K. De Brabander, *Org. Lett.* **2006**, *8*, 4907–4910; f) H. Qian, X. Han, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 9536–9537; g) D. W. Lucey, J. D. Atwood, *Organometallics* **2002**, *21*, 2481–2490.

[12] For an excellent account on σ- and π-electrophilic Lewis acids, see: Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817–7831.

[13] Formation of approximately one equivalent of the corresponding aniline derivative is observed in all these reactions. The role of dienes **11** as intermediates of the reaction is supported by the isolation, in some particular cases, of dienes analogous to **11** in reactions performed under the standard conditions. Moreover, diene **11** was synthesized by an independent method and subjected to the reaction conditions to give compound **4j** in 90% yield.

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