# Gold(I)-catalyzed formation of dihydroquinolines and indoles from *N*-aminophenyl propargyl malonates†‡

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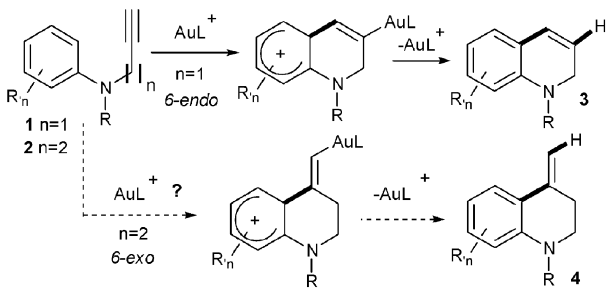
**The use of [XPhosAu(NCMe)]$SbF_6$ in nitromethane at 100 °C allows the rapid and efficient formation of variously substituted dihydroquinolines, which can be subsequently converted into indoles by a rare photochemical rearrangement.**

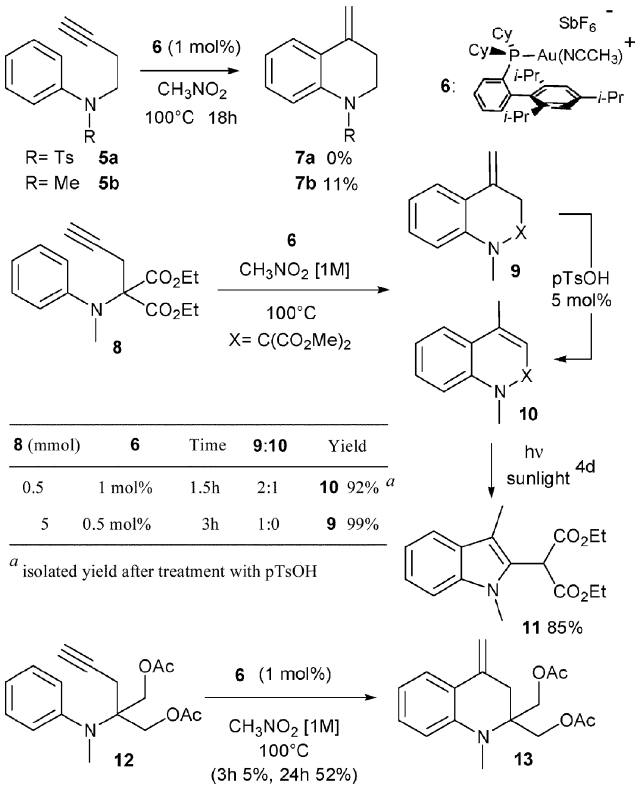


Gold catalysis has proven during the last decade to be a powerful synthetic tool for the synthesis of a large variety of nitrogen containing heterocycles.[1] Among the different strategies employed, those based on the use of an intramolecular gold-catalyzed hydroarylation reaction are particularly attractive as they allow the easy creation of a new C–C bond by the nucleophilic addition of an aryl unit onto an insaturation.[2] This approach has been applied for instance to the formation of dihydroquinolines **3** by a gold-catalyzed 6-*endo* cyclization of *N*-propargyl anilines **1** (Scheme 1, $n = 1$).[3]

Following our own interest in gold catalysis, we wondered if the homologous *N*-butynyl anilines **2** might be valuable substrates for the synthesis of the isomeric *exo*-methylene tetrahydroquinolines **4** *via*, in this case, a 6-*exo* cyclization (Scheme 1, $n = 2$). *N*-Butynyl tosylaniline **5a**, was first chosen as a model substrate for this study (Scheme 2).[3a,b] However, no cyclized product **7a** could be observed in this case whatever the catalyst, the solvent or the temperature used.[4] The transformation was next attempted with substrate **5b** where the aryl moiety is more nucleophilic. An encouraging 11% yield of **7b** was obtained when the reaction was conducted in nitromethane at 100 °C with [XPhosAu(NCMe)]$SbF_6$ (**6**) as the catalyst.[5] Aniline derivative **8**, proved to be a more useful substrate since its treatment with 1 mol% of **6** in nitromethane at 100 °C for 1.5 h led to the formation of two cyclized products namely *exo*-methylene tetrahydroquinoline **9** and dihydroquinoline **10** in a 2 : 1 ratio (Scheme 2).[6,7]




**Scheme 1** Au-mediated synthetic approaches to hydroquinolines.




| 8 (mmol) | 6 | Time | 9:10 | Yield |
|---|---|---|---|---|
| 0.5 | 1 mol% | 1.5h | 2:1 | **10** 92% [a] |
| 5 | 0.5 mol% | 3h | 1:0 | **9** 99% |

[a] isolated yield after treatment with pTsOH

**Scheme 2** Preliminary studies.

Subsequent treatment of the crude reaction mixture with $p$-TsOH (5 mol%) led to the rapid isomerization of **9** into **10**, which was finally isolated in 92% yield.[8] The reaction could also be efficiently performed (99%) on a 5 mmol scale with a reduced loading of catalyst (0.5 mol%). Under these conditions and by carefully monitoring the reaction, it was even possible to suppress the formation of isomeric compound **10**. The presence of the malonate moiety in substrate **8** appears to be crucial for the efficient formation of the hydroarylation product. The replacement of the esters of the malonate moiety by two acetoxymethyl groups (substrate **12**) had a negative effect, as only 5% of the corresponding hydroarylation product was produced after 3 h of reaction.[9] Dihydroquinoline **10** was not very stable, and we were surprised to observe its slow conversion into indole **11** when a chloroform solution of **10** was exposed to sunlight (Scheme 2).[10,11]

This unexpected photochemical rearrangement is particularly interesting since indole **11** could be formed in high yield in only two steps from the readily available *N*-aminophenyl propargyl malonate **8**.

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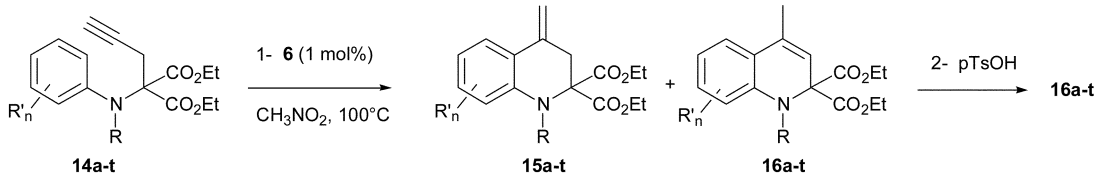
**Table 1** Scope of the hydroarylation process[a]



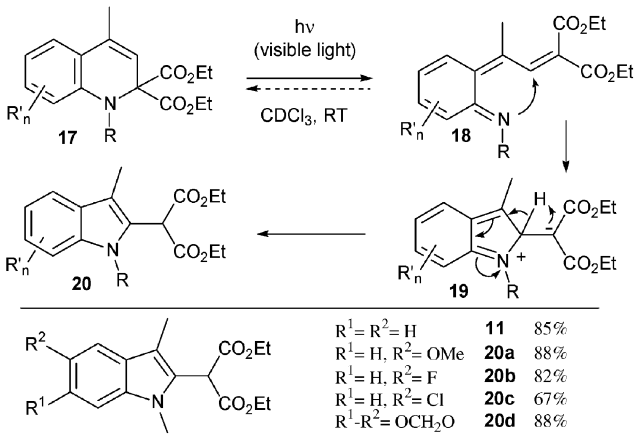

| Entry | Substrate | | Time [b] | (15:16) [c] | Product | Yield 16 [d] |
|---|---|---|---|---|---|---|
| 1 | R= Et | **14a** | 20 min | 1:0 | **16a** | 97% |
| 2 [e] | R= Ph | **14b** | 30 min | 2.2:1 | **16b** | 86% |
| 3 | n= 1 | **14c** | 18 h | 1.1:1 | **16c** | 99% |
| 4 | n= 2 | **14d** | 30 min | 2:1 | **16d** | 94% |
| 5 | R= OMe | **14e** | 50 min | 1:0 | **16e** | 95% |
| 6 | R= OBu | **14f** | 1.5 h | 1:0 | **16f** | 99% |
| 7 | R= $OCF_3$ | **14g** | 30 min | 1:0 | **16g** | 91% |
| 8 | R= F | **14h** | 18 h | 1:0 | **16h** | 84% |
| 9 | R= Cl | **14i** | 7 h | 1:0 | **16i** | 85% |
| 10 | R= Br | **14j** | 30 min | 1:0 | **16j** | 97% |
| 11 | R= I | **14k** | 40 min | 1:0 | **16k** | 97% |
| 12 | R= $CO_2Et$ | **14l** | 4 h | 1:0 | **16l** | 97% |
| 13 | R= CN | **14m** | 30 min | 1:0 | **16m** | 94% |
| 14 | | **14n** | 1.5h | 1:0 | **15n** | 88% [f] |
| 15 | $R^1$, $R^2$= OMe | **14o** | 30 min | 0:1 | **16o** | 75% |
| 16 | $R^1$-$R^2$= $OCH_2O$ | **14p** | 20 min | 0:1 | **16p** | 53% |
| 17 | | **14q** | 30 min | 1:0 | **15q** | 93% [f] |
| 18 | R= OMe | **14r** | 30 min | ND | **16r**:**16'r**= 1.7:1 | 93% [g] |
| 19 | R= Et | **14s** | 30 min | ND | **16s**:**16's**= 1.5:1 | 71% [g] |
| 20 [e] | R= $CF_3$ | **14t** | 5 h | ND | **16t**:**16't**= 1:1 | 90% [g] |

$R^1$=R, $R^2$=H **16r-s**

$R^1$=H, $R^2$=R **16'r-s**

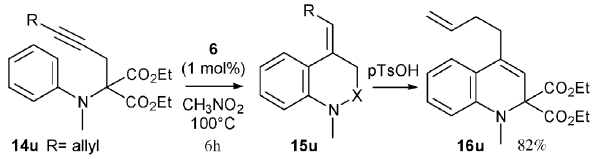
[a] *Reaction conditions*: step 1: **14** (1 equiv.), [XPhosAu(NCMe)]$SbF_6$ (**6**) (0.01 equiv.) in refluxing $CH_3NO_2$ (1 M); step 2: *p*-TsOH (0.05 equiv.) in $CH_2Cl_2$ (0.1 M) at rt or reflux. [b] Reaction time for step 1. [c] Determined by $^1H$ NMR spectroscopy of the crude reaction mixture after step 1. [d] Isolated yields after step 2. [e] **6** (2 mol%). [f] Yield of *exo*-methylene compound **15**. Isomerization was incomplete. [g] Global yield of the isomeric mixture (**16** + **16′**).

A series of diversely substituted *N*-aminophenyl propargyl malonates **14a–t** were then synthesized[4] and reacted under the same reaction conditions (1 mol% of **6** in nitromethane at 100 °C) to determine the scope of the hydroarylation process. The results of this study are compiled in Table 1. The transformation proved to be efficient and various dihydroquinolines **16a–t** were rapidly obtained in yields ranging from 53 to 99%. The gold catalyzed hydroarylation process selectively furnished the *exo*-methylene compounds **15** with the exception of substrates **14b–d**, which resulted in isomeric mixtures of **15b–d** and **16b–d** (entries 2–4). In the case of the electron rich substrates **14o** and **14p** (entries 15 and 16), the gold catalyzed process directly produced the corresponding dihydroquinolines **16o** and **16p**, as the result of a more favourable gold-catalyzed isomerization of the *exo*-methylene. Various substitutents on the nitrogen atom such as an alkyl group (entry 1), a phenyl ring (entry 2) or a cycloalkyl unit linked to the aromatic ring (entries 3 and 4) were tolerated. The reaction was also compatible with a wide range of functional groups onto the aromatic ring such as an electron donating ether group (entries 5–7, 15, 16 and 18), a halogen atom (entries 8–11 and 14), or an electron withdrawing ester (entry 12), cyano (entry 13) or trifluoromethyl (entry 20) group. Notably, the efficiency and the rapidity of the reaction were not markedly dependent on the electronic nature of the substituent (compare entries 5–13) or its position on the aromatic ring since *ortho* (entries 3, 4 and 14), *meta* (entries 15–20) or *para* (entries 5–13) substituted aryl




**Scheme 3** Photochemical rearrangement to indoles.

substrates reacted equally well. While compounds **14o–q**, possessing two substituents at the *meta* and *para* positions of the aniline moiety only produced dihydroquinolines **16o–q** (entries 15–17), the reaction proved to be completely unselective in the case of substrates **14r–t** (entries 18–20).[12] The transformation could also be applied with the same efficiency to substituted alkyne **14u** (eqn (1)). The selectivity of the reaction was complete as the result of an *anti* addition of the nucleophilic aryl moiety onto the gold-activated alkyne.




(1)

We finally turned our attention to the rearrangement of the dihydroquinolines into the corresponding indoles, as initially observed for compound **10**. A series of dihydroquinolines were indeed similarly converted into the corresponding indoles **20a–d** by simple exposure to sunlight (67–88%). A mechanism for this remarkable ring contraction is proposed in Scheme 3. Upon irradiation, dihydroquinoline **17** undergoes presumably an electrocyclic ring opening leading to intermediate **18**. A subsequent nucleophilic attack of the nitrogen atom onto the electrophilic alkylidene malonate moiety, energetically driven by the re-aromatisation of the benzene ring, furnishes a zwitterionic species **19** which finally collapses into indole **20**.[13]

In summary, we have developed an efficient synthesis of *exo*-methylene tetrahydroquinolines and dihydroquinolines from readily accessible *N*-aminophenyl propargyl malonates. The hydroarylation process, which could be performed with a low loading of catalyst (1 mol%), proved to be rapid and general allowing the presence of a plethora of functional groups on the aromatic ring. Furthermore, the dihydroquinolines were shown to easily rearrange to functionalized indoles under photochemical conditions thus expanding the general synthetic utility of the approach.

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## Notes and references


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4 See ESI‡ for more details.

5 For the use of catalyst **6** in $CH_3NO_2$, see: I. D. Jurberg, Y. Odabachian and F. Gagosz, *J. Am. Chem. Soc.*, 2010, **132**, 3543.

6 The use of catalyst **6** in $CH_3NO_2$ appears to be the catalytic system of choice as it stabilizes the catalyst and leads to a rapid and generally selective formation of **15** for the series of substrates studied.

7 The **9**:**10** ratio slowly evolves upon prolonged reaction time. For this alkene isomerisation, see: A. S. K. Hashmi, M. C. Blanco, E. Kurpejovic, W. Frey and J. W. Bats, *Adv. Synth. Catal.*, 2006, **348**, 709.

8 Dihydroquinoline **10** was unstable in the presence of silica. A simple basic work-up followed, if necessary, by a rapid filtration through a pad of silica was used to obtain the product in pure form.

9 The malonate moiety plays multiple roles in this transformation: it induces a Thorpe–Ingold effect resulting in a more favorable cyclization while limiting the coordination of the gold catalyst with the nitrogen atom probably through steric and electronic effects.

10 The electrocyclic ring-opening of 1,2-dihydroquinolines is a rare process, see: (*a*) M. Ikeda, S. Matsugashita, H. Ishibashi and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 1973, 922; (*b*) M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 1974, 433; (*c*) M. Ikeda, S. Matsugashita, F. Tabusa and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1166.

11 No reaction took place under thermal conditions (toluene, 110 °C) or in the presence of a Lewis acid ($Yb(OTf)_3$, rt). Compound **10** was stable in the absence of light.

12 The hydroarylation seems to be little influenced by the electronic nature or the steric hindrance of a *meta* substituent.

13 Formation of **20** may also be explained by the intermediate formation of an allenylidene malonate from **18** (see ref. 10).




 