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Synthetic Methods

Access to 1,2-Dihydroisoquinolines through Gold-Catalyzed Formal [4+2] Cycloaddition

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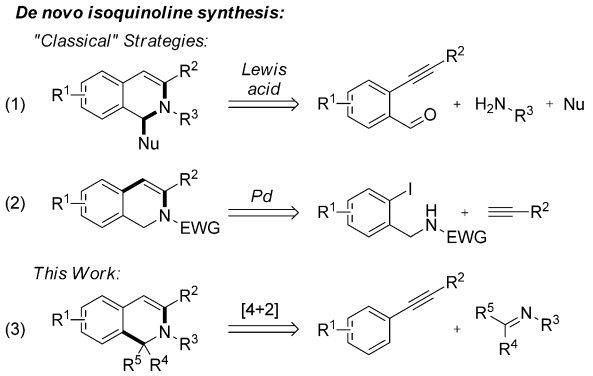
Abstract: A new synthetic route to the privileged 1,2-dihydroisoquinolines is reported. This method, which relies on a gold-catalyzed formal [4+2] cycloaddition between ynamides and imines, provides a new retrosynthetic disconnection of the 1,2-dihydroisoquinoline core by installing the 1,8a C–C and 2,3 C–N bonds in one step. Both aldimines and ketimines can be used as substrates. In addition, one example of dihydrofuropyridine synthesis is also demonstrated.

The 1,2-dihydroisoquinoline core represents a privileged structure encountered in many natural products, as well as molecules exhibiting promising bioactivities. Hence, the synthesis of this motif has been of high interest for the organic-synthesis community.[1] In general, two different approaches to these structural targets have been developed: a) functionalization of the parent isoquinoline or b) de novo synthesis of the 1,2-dihydroisoquinoline. Significant progress has been made for the first approach, in which either the C1 and C2 substituents were introduced through a Reissert-type reaction, or alternatively the parent isoquinoline can be reduced selectively to the 1,2-dihydroisoquinoline.[2] These strategies inherently require that the desired substituents are already present on the parent isoquinoline. Therefore, a de novo approach might provide easier access to more diversely functionalized heterocycles. In general, the de novo synthesis of functionalized 1,2-dihydroisoquinolines is limited to variations of the transition-metal-catalyzed 6-*endo* cyclization of *ortho*-alkynylaryl aldimines either as the substrate or made in situ from the aldehyde (Scheme 1, Eq. (1)); however, other strategies including the Larock dihydroisoquinoline synthesis have also been developed.[3,4] Interestingly, there is no existing method for de novo synthesis of 1,2-dihydroisoquinolines installing the 1,8a C–C bond and 2,3 C–N bond in one step (Scheme 1, Eq. (3). The successful development of such a formal [4+2] cycloaddition would therefore add significantly to the arsenal of disconnections for 1,2-dihydroisoquinolines.



Scheme 1. New retrosynthetic disconnection of the 1,2-dihydroisoquinoline core. EWG = electron-withdrawing group.

Over the last decade, the tremendous potential of homogeneous gold catalysis has been investigated, and new reactivities are still being discovered.[5] Inspired by the gold-catalyzed [4+2] cycloadditions between alkenes and ynamides developed by Liu et al., we envisaged the possibility to develop the first method for the above-mentioned disconnection of the 1,2-dihydroisoquinoline core as a mean for the synthesis of highly substituted 1,2-dihydroisoquinolines.[6,7] While not only providing a new route to this important heterocycle, the proposed strategy would also display complete atom economy with no pre-functionalization of the aryl moiety necessary.

A few examples of interception of gold–carbene intermediates with imines followed by cyclization have been published including a new synthesis of dihydro-γ-carbolines.[8] However, no direct [4+2] cycloadditions between 1,3-enynes and imines have been reported.[9]

In 2011, we reported the dimerization of ynamides and isolated the products arising from a formal [4+2] cycloaddition between the triple bond of one ynamide with the alkynylaryl moiety of another ynamide.[10b] As part of our continued interest in ynamides and gold catalysis, we decided to use ynamides as substrates for the proposed transformation.[10,11]

Our initial investigations were encouraging as 5 mol% $IPrAuNTf_2$ (IPr = 1,3-bis(diisopropyl phenyl) imidazole-2-ylidene) in 1,2-dichloroethane (DCE) at 60 °C led to clean conversion to the desired dihydroisoquinoline **3a**, which could be isolated in a satisfactory yield of 96% (Table 1, entry 1). The structure of **3a** was confirmed by X-ray analysis as depicted in Figure 1. At

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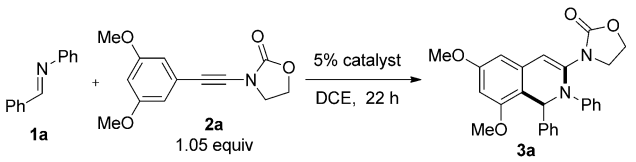
Table 1. Optimization of the 1,2-dihydroisoquinoline synthesis.



Entry	Catalyst	T [°C]	Yield [%][a]
1	$IPrAuNTf_2$	60	100 (96)
2	$IPrAuNTf_2$	RT	60
3	$(Ph_3P)AuNTf_2$	60	100
4	$PicAuCl_2$	60	93
5	$AgNTf_2$	60	0
6	$HNTf_2$	60	0
7	none	60	0

[a] Determined by ^1H NMR spectroscopy of the crude reaction mixture by using 1,3,5-trimethoxybenzene as internal standard. Isolated yield after column chromatography in parenthesis.

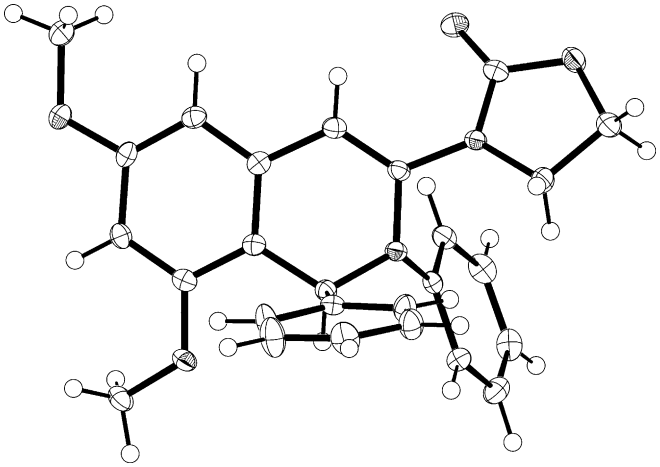
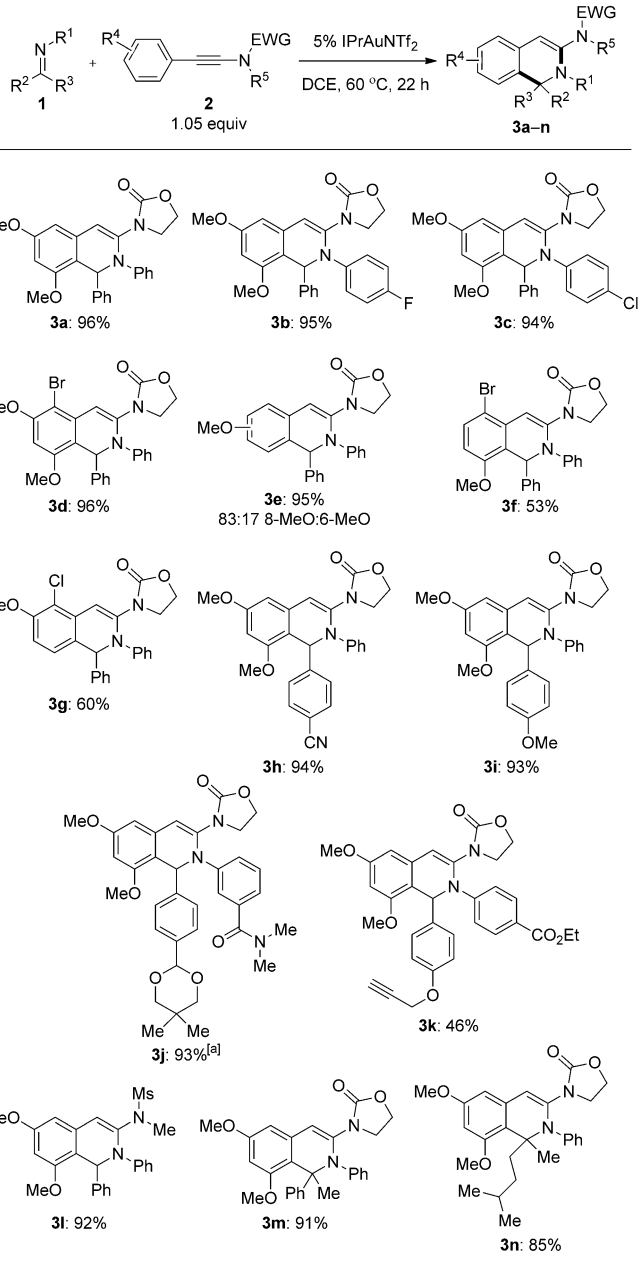


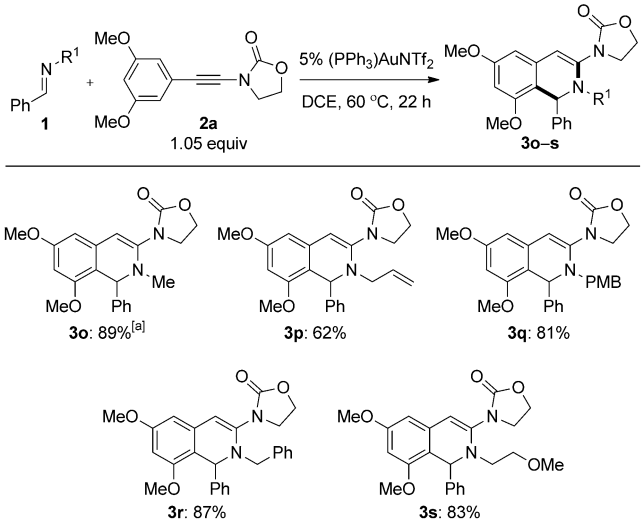
Figure 1. X-ray structure of **3a**.

room temperature, lower conversion and yield was obtained (Table 1, entry 2). The use of Gagosz' catalyst, $(Ph_3P)AuNTf_2$, also led to clean conversion to **3a** (Table 1, entry 3); however, for ynamides with less electron-rich aryls, $IPrAuNTf_2$ provided slightly higher yields and this catalyst was therefore chosen for the investigation of the substrate scope.[12] Examining the gold(III) catalyst, $PicAuCl_2$ (Pic = picolinato), a small drop in yield was observed compared to the two gold(I) catalysts (Table 1, entry 4). Both $AgNTf_2$ and $HNTf_2$ were completely ineffective as catalysts for the formal [4+2] cycloaddition (Table 1, entries 5 and 6), and no product formation was observed in the absence of a catalyst (Table 1, entry 7).

With the optimized reaction conditions established, we started investigating the substrate scope with *N*-aryl imines (Scheme 2). Halogen substituents (F, Cl, Br) in different positions of the substrates still led to high yields of the desired products when two methoxy groups were present on the ynamide **3b**–**d**. For the ynamide with only one methoxy group, there was no erosion in yield, and good regioselectivity was observed favoring the 8-methoxy product **3e**. With only one methoxy group, bromides and chlorides were also tolerated, although a slight decrease in the yield was observed for **3f** and **g**. This corresponds with the less nucleophilic character of the aryl moiety of these ynamides. Other functional groups than halides were tolerated including cyano, methoxy, amide, ester, ether, alkyne, and acetal groups as illustrated with the products **3h**–**k**. Employing a mesyl instead of the alkoxycarbonyl group as the electron-withdrawing substituent did not affect the reaction outcome (**3l**). Furthermore, when the reaction was performed with ketimines instead of aldimines, the products were again obtained in a high yields, as shown with



Scheme 2. Substrate scope for the 1,2-dihydroisoquinoline synthesis with *N*-aryl imines. The yields given are for the isolated product. [a] The reaction was performed at 80 °C.



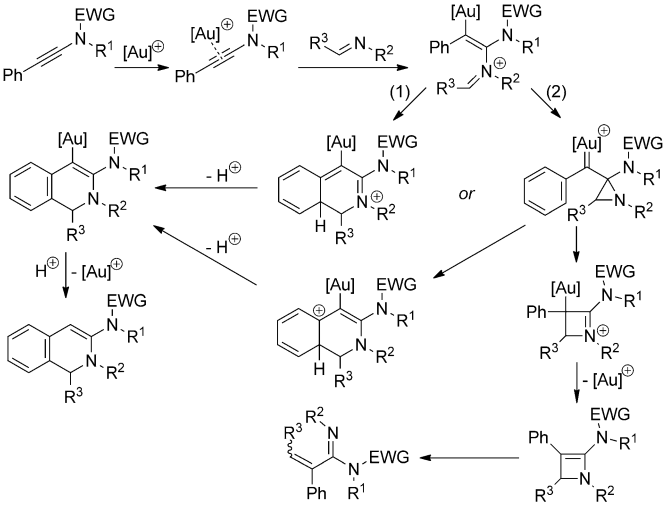
Scheme 3. Substrate scope for the 1,2-dihydroisoquinoline synthesis with *N*-alkyl imines. The yields given are for the isolated product. PMB = *para*-methoxybenzyl. [a] The reaction was performed with 1% $(PPh_3)AuNTf_2$.

3m and **n**. Both dialkyl and arylalkyl imines gave the desired 1,2-dihydroisoquinoline with quaternary centers.

Next, we turned our attention to *N*-alkyl imines (Scheme 3). For these substrates, $(Ph_3P)AuNTf_2$ turned out to be the superior catalyst, but otherwise the reaction conditions remained unchanged. We were pleased to see that the nitrogen substituents, such as methyl (**3o**), allyl (**3p**), *para*-methoxybenzyl (**3q**), and benzyl (**3r**), as well as an alkyl ether on a two-carbon linker (**3s**), were well tolerated.

For the unsubstituted phenyl ring in the terminal position of the ynamide, byproduct formation was observed along with the desired product (Scheme 4a). The byproducts were identified as the aza-enyne metathesis products **4a** and **5**, which are the typical products when Brønsted acid catalysis is applied to these substrates.[13] However, in our case, the ratio of product to byproducts was unchanged in the presence of stoichiometric amounts of $NaHCO_3$, indicating that these products are more likely formed by gold catalysis instead of Brønsted acid catalysis under our reaction conditions.[14] Interestingly, when the electron-donating groups were removed from the aromatic ring of the ynamide, and an *N*-alkyl imine was employed, byproduct **4** could be obtained in excellent yield after a simple optimization (Scheme 4b). The yield of the product was the same as that with the addition of stoichiometric amounts of $NaHCO_3$. This result further proves that the reaction is indeed catalyzed by gold instead of a Brønsted acid.

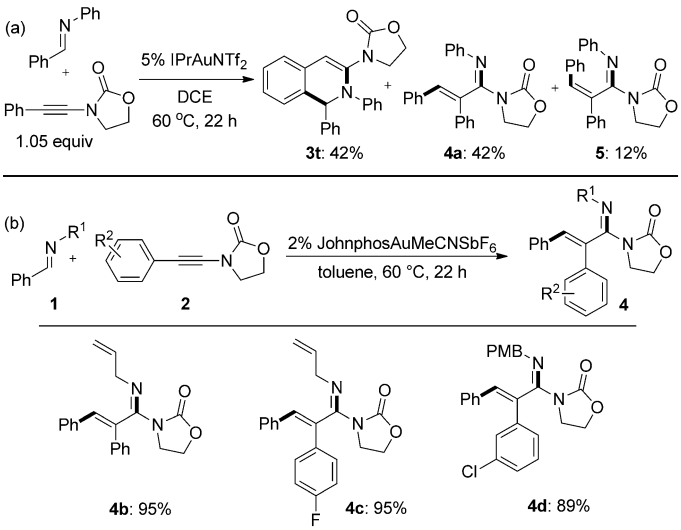
A mechanistic proposal for the formal [4+2] cycloadditions leading to 1,2-dihydroisoquinolines is shown in Scheme 5. Activation of the triple bond in the ynamide by the gold catalyst would be followed by addition of the imine through nitrogen.



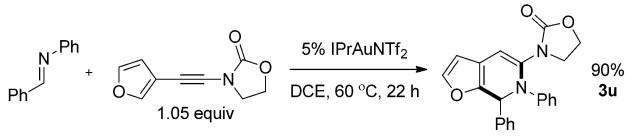
Scheme 5. Proposed mechanism for dihydroisoquinoline and byproduct formation.

Two possible pathways for the generated iminium intermediate can then be envisioned. The direct trapping of the iminium species by the aromatic ring would give the dihydroisoquinoline core with only a deprotonation and protodeauration necessary to generate the final product (path 1). Alternatively, in analogy to the mechanism for the two different reactions between alkenes and alkynes reported by Liu et al. and Shin et al., the formation of a gold carbene and an aziridine can be proposed (path 2).[6,14] Although this intermediate might also be on the path to the dihydroisoquinolines, it can explain the byproduct formation through a 1,2-migration to the gold carbene. Elimination of the gold fragment would lead to a dihydroazete, which can open in a 4π electrocyclic ring opening generating the byproducts.

Finally, to further expand the synthetic utility of the formal [4+2] cycloaddition, an ynamide with a furan in the terminal position was subjected to the optimized reaction conditions



Scheme 4. a) Reaction products with a less nucleophilic aromatic ring. b) Reaction of ynamides without electron-rich groups in the aromatic ring with *N*-alkyl imines. The yields given are for the isolated products. PMB = *p*-methoxybenzyl.



Scheme 6. Extension to dihydrofuropyridine synthesis.

(Scheme 6). This led directly to the corresponding dihydrofuropyridine **3u** in a high yield.

In summary, we have developed the first method for the simultaneous formation of the 1,8a C–C bond and 2,3 C–N bond of 1,2-dihydroisoquinolines thereby adding a new disconnection to this important heterocycle. This de novo methodology displays good functional-group tolerance and works well for both aldimines and ketimines, as well as both *N*-aryl imines and *N*-alkyl imines. Furthermore, one example of the extension to the synthesis of a dihydrofuropyridine was demonstrated.

Experimental Section

Synthesis of 3-(6,8-dimethoxy-1,2-diphenyl-1,2-dihydroisoquinolin-3-yl)oxazolidin-2-one (3a, Scheme 2)

To a vial (4 mL) in an argon-filled glovebox were added $IPrAuNTf_2$ (5 mol%, 0.01 mmol, 8.7 mg), ynamide (**2a**, 0.21 mmol, 51.9 mg, 1.05 equiv), and imine (**1a**, 0.20 mmol, 36.2 mg, 1.00 equiv) followed by DCE (0.8 mL). The vial was sealed, and the reaction mixture was stirred 22 h at 60 °C outside the glovebox. The reaction mixture was allowed to cool to RT and then concentrated in vacuo. The crude oil was purified by flash chromatography (1% Et_2O in CH_2Cl_2) giving the 1,2-dihydroisoquinoline **3a** in a 96% yield (82.0 mg). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.21$ (m, 9H), 7.08 (t, $J = 7.2$ Hz, 1H), 6.48 (d, $J = 2.4$ Hz, 1H), 6.42 (s, 1H), 6.35 (d, $J = 2.4$ Hz, 1H), 6.21 (s, 1H), 4.15 (q, $J = 8.4$ Hz, 1H), 4.05 (q, $J = 8.4$ Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 3.48 ppm (t, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.3$, 156.4, 155.8, 146.0, 142.4, 134.5, 133.7, 129.7 (2C), 128.2 (2C), 127.5, 127.0 (2C), 123.7, 121.0 (2C), 111.7, 106.3, 101.2, 97.1, 61.9, 61.5, 55.54, 55.50, 44.8 ppm. HRMS: $C_{26}H_{24}N_2O_4$: calcd 429.1809 $[M+H^+]$; found: 429.1813.

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Keywords: cycloaddition · homogeneous catalysis · gold · heterocycles · ynamides

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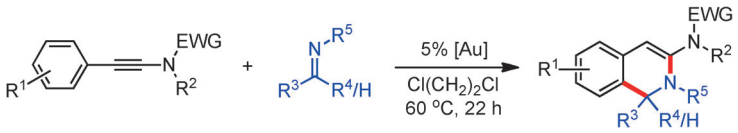
Access to 1,2-Dihydroisoquinolines through Gold-Catalyzed Formal [4+2] Cycloaddition



Heterocycles: A new synthetic route to the privileged 1,2-dihydroisoquinolines is reported. This method, which relies on a gold-catalyzed formal [4+2] cycloaddition between ynamides and imines, provides a new retrosynthetic disconnection of the 1,2-dihydroisoquinoline core by installing the 1,8a C–C and 2,3 C–N bonds in one step. Both aldimines and ketimines can be used as substrates. In addition, one example of dihydrofuropyridine synthesis is also demonstrated (see scheme).