Heterocycles Hot Paper

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Gold-Catalyzed Synthesis of Functionalized Pyridines by Using 2*H*-Azirines as Synthetic Equivalents of Alkenyl Nitrenes**

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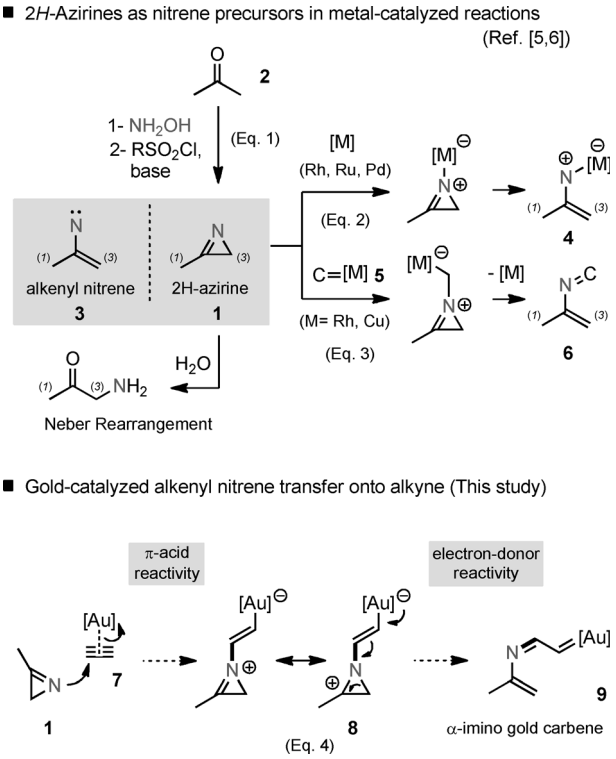
Dedicated to Professor Albert Padwa

Abstract: *2H-Azirines are easily synthesized from the corresponding ketones and, despite possessing a C=N bond embedded in a strained three-membered cycle, they are sufficiently stable to be isolated, stored, and manipulated. 2H-Azirines can be regarded as valuable synthetic equivalents of alkenyl nitrenes, however, reactions capitalizing on the cyclic strain of the heterocyclic motif and involving the cleavage of the C–N single bond remain surprisingly limited. A gold-catalyzed reaction that allows the formation of polysubstituted functionalized pyridines from easily accessible 2-propargyl 2H-azirine derivatives was developed. This transformation, which corresponds to an unprecedented intramolecular transfer of an alkenyl nitrene to an alkyne, proceeds with low catalyst loading, is efficient, and exhibits a high functional-group tolerance and a wide substrate scope.*

The unusual heterocyclic motifs 2*H*-Azirines[1] (**1**) are mostly known as reactive intermediates in the Neber rearrangement,[2] a useful transformation that allows the installation of an amino group at positions α to a ketone. 2*H*-Azirines can be easily synthesized from the corresponding ketones **2** by following a reliable two-step procedure [Scheme 1, Eq. (1)]. While they possess an intriguing structure featuring a C=N bond embedded in a strained three-membered cycle, they are sufficiently stable to be isolated, stored, and manipulated.

Of the various transformations of 2*H*-azirines that have been reported to date,[1,3] those capitalizing on the cyclic strain of the heterocyclic motif and involving the cleavage of the C–N single bond remain surprisingly limited. 2*H*-Azirines can, however, be regarded as valuable synthetic equivalents of alkenyl nitrenes (**3**)[1] and therefore deserve more consideration in view of the recent developments in metal-mediated nitrene chemistry.[4] To date, only two modes of reactivity involving 2*H*-azirines as synthetic equivalents of nitrenes have been described: a) the direct interaction of **1** with a metal, thus leading to the formation of a metal–nitrene complex of type **4** [Scheme 1, Eq. (2)][5]; and b) the reaction between a metal–carbene complex (**5**) and **1** to produce an azadiene such as **6** [Scheme 1, Eq. (3)].[6] In this context, and following our continuing interest in gold catalysis,[7,8] we considered the possibility of performing an alternative and unprecedented alkenyl nitrene transfer to alkynes[9] by taking advantage of the π-acid and electron-donor properties of gold complexes [Scheme 1, Eq. (4)].[7] In such a process, the nucleophilic addition of **1** to a gold-activated alkyne (**7**) would furnish the aziridinium species **8**, which would then evolve into the corresponding reactive α-imino gold–carbene intermediate **9**. We report herein the successful implementation of this mechanistic design to the synthesis of functionalized pyridines[10] **11** from 2-propargyl 2*H*-azirine derivatives **10** [Scheme 2, Equation (5)].[11] These substrates could be obtained in an efficient and modular manner following the synthetic routes shown in Equations (6) and (7) in Scheme 2.

Our investigations started with 2*H*-azirine **10a**. The gold-catalyzed cycloisomerization of **10a** to give pyridine **11a** was chosen as a model to evaluate the feasibility of the alkenyl nitrene transfer to an alkyne in its intramolecular version.



Scheme 1. 2*H*-Azirines as synthetic equivalents of nitrenes in metal-mediated transformations and the design of a gold-catalyzed transfer of alkenyl nitrenes to alkynes.

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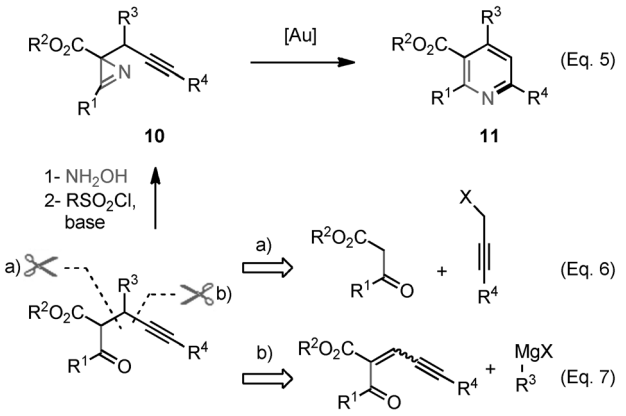
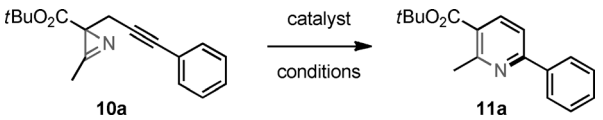


Scheme 2. A synthetic route to functionalized pyridines.

Compound **10a**, which could be conveniently obtained by a four-step sequence from *tert*-butyl acetoacetate,[12] was first treated with the simple $[(Ph_3P)Au]NTf_2$ complex[13] (5 mol%) in $CDCl_3$ at 50 °C and the reaction was monitored by ^1H NMR spectroscopy (Table 1, Entry 1). We were pleased to observe the slow but clean conversion of **10a** into the desired pyridine **11a**, which gradually accumulated to reach a moderate yield of 40% after 3 h. A series of other gold complexes possessing various electronic and steric properties were then screened in an attempt to increase both the rate and the yield of the reaction. The main results of this study are compiled in Entries 2–8 of Table 1. While $[(JohnPhos)Au]NTf_2$, $[(IPr)Au]NTf_2$ and the phosphite-based gold(I) complex **12** proved to be less catalytically active (Table 1, Entries 2–4), a remarkable improvement was made when complexes possessing bulky ligands of the XPhos family were employed (Table 1, Entries 5 and 6). The best result was obtained with $[(t\text{BuXPhos})Au]NTf_2$ (**13**), which allowed the complete conversion of **10a** in 3 h and the formation of **11a** in an excellent yield of 95% (Table 1, Entry 6). An additional improvement was subsequently achieved: working at a lower catalyst loading of 2 mol% in refluxing 1,2-dichloroethane reduced the reaction time to 1.5 h while maintaining the efficiency of the process (Table 1, Entry 7). Under these experimental conditions, pyridine **11a** could be isolated in an optimal yield of 90%. Additional control experiments were also carried out to show that the transformation could not be performed by using $AgNTf_2$ or $HNTf_2$ as the catalyst, or under simple thermal conditions (Table 1, Entries 9–12).[14]

Table 1: First attempts at cyclization with azirine **10a** and optimization of the catalytic system.[a]



10a **11a**

Entry	Catalyst[b]	Solvent	*T* [°C]	*t* [h]	Conv.[c] [%]	Yield[d] [%]
1	$[Ph_3PAu]NTf_2$	$CDCl_3$	50	3	42	40
2	$[(JohnPhos)Au]NTf_2$	$CDCl_3$	50	3	33	28
3	$[(IPr)Au]NTf_2$	$CDCl_3$	50	3	18	17
4	$[(ArO)_3PAu]NTf_2$[e]	$CDCl_3$	50	3	35	32
5	$[(XPhos)Au]NTf_2$	$CDCl_3$	50	3	90	82
6	$[(t\text{BuXPhos})Au]NTf_2$	$CDCl_3$	50	3	100	95
7	$[(t\text{BuXPhos})Au]NTf_2$[f]	$(CH_2Cl)_2$[g]	85	1.5	100	95 (90%)[h]
8	$AuCl_3$	CD_3CN	50	3	8	7
9	$AgNTf_2$	$CDCl_3$	50	4	–[i]	–
10	$HNTf_2$	$CDCl_3$	50	4	–[i]	–
11	–	$CDCl_3$	50	4	–[i]	–
12	–	toluene	110	4	–[i]	–

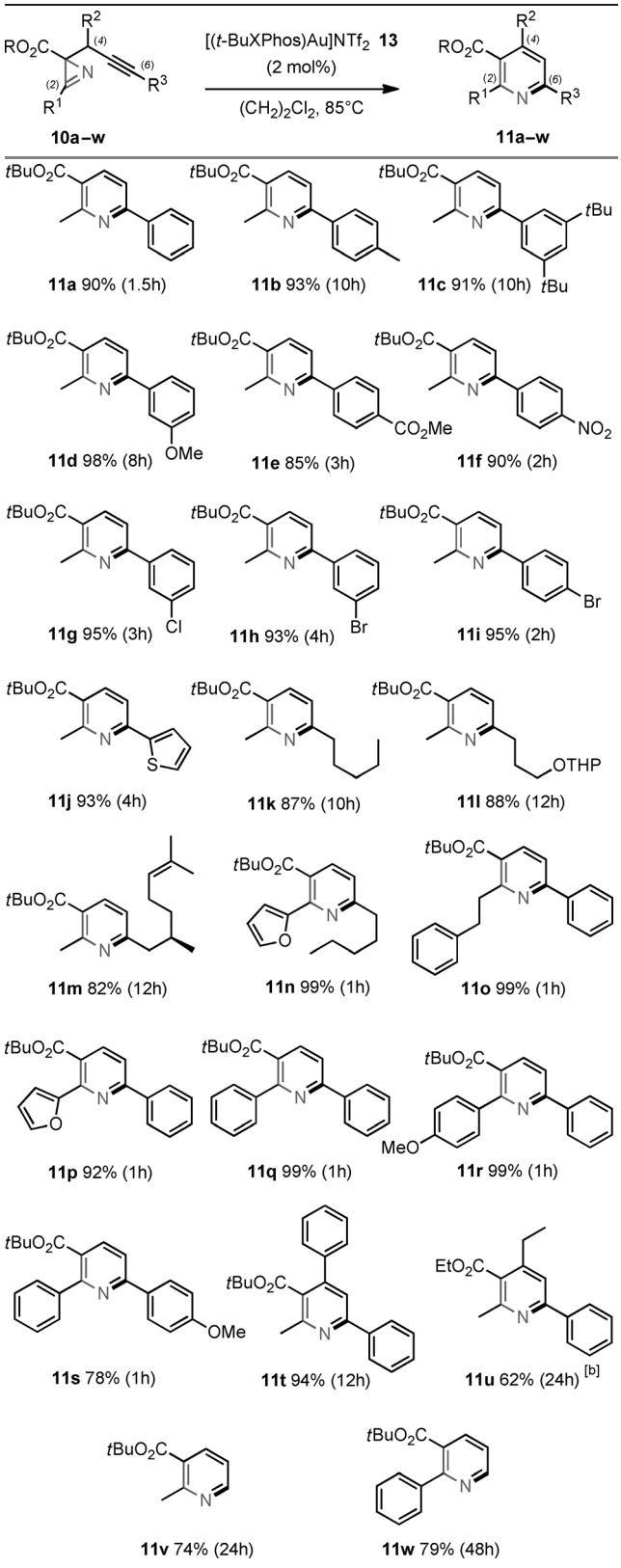
[a] Substrate concentration: 0.07 M. [b] Catalyst loading 5 mol% except for Entry 7. [c] Determined by ^1H NMR spectroscopy. [d] Yield measured by NMR spectroscopy. [e] Ar = 2,6-$(t\text{Bu})_2$-C_6H_3. [f] Catalyst loading 2 mol%. [g] Substrate concentration: 0.1 M. [h] Yield of isolated product. [i] No conversion observed by ^1H NMR spectroscopy. Tf = triflate, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

The optimal catalytic conditions noted in Table 1, Entry 7 (2 mol% of **13** in $(CH_2)_2Cl_2$ at 85 °C) were then applied to a range of 2-propargyl 2*H*-azirine derivatives (**10a–w**) to determine the scope of the reaction. As seen from the results collected in Table 2, the transformation proved to be extremely general and the corresponding functionalized pyridines **11a–w** could be obtained in good to excellent yields (62–99%). The substrates were completely consumed in generally less than 10 h with the exception of terminal alkynes (**10v,w**), for which an extended reaction time was required. The reaction could be performed with substrates possessing aryl groups with either electron-donating (**11d,r,s**) or electron-withdrawing (**11e,f**) substituents, heteroaromatic moieties such as a furan (**11n,p**) or thiophene (**11j**), or alkyl chains (**11k–n**). Substitutions were tolerated at the alkyne terminus ($C_{(6)}$), at the propargylic position ($C_{(4)}$), and on the azirine motif ($C_{(2)}$) of the substrates, thus allowing the formation even of tetrasubstituted pyridines (**11t,u**).

The transformation also proved to be compatible with the presence of various commonly employed functionalities such as esters (**11a–w**), halogen atoms (**11g–i**), ketals (**11l**), nitro groups (**11f**), and alkenes (**11m**). A series of general comments can be made regarding the reactivity of the substrates. First, it is notable that the reaction is selective and that despite the use of regular 1,2-dichloroethane, no trace of amino ketone products resulting from a Neber rearrangement[2] could be observed. Nor could by-products resulting from a potentially competitive gold-catalyzed nucleophilic addition of the *tert*-butyloxycarbonyl group on the alkyne be detected.[15]

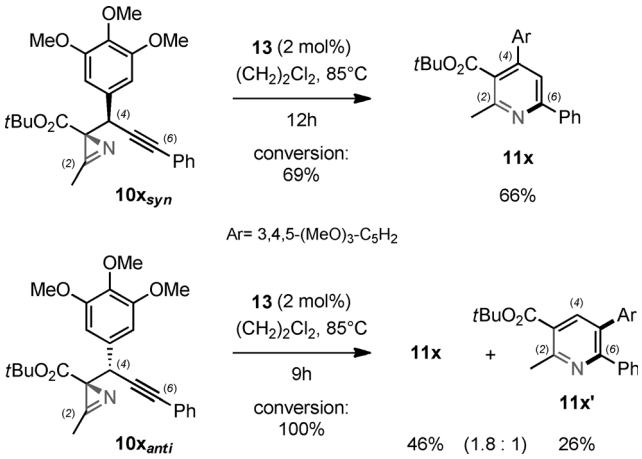
While no general rule can be established, it is also interesting to note that substrates such as **10k–m**, which possess alkyl substituents both at the alkyne terminus ($C_{(6)}$) and on the azirine moiety ($C_{(2)}$), tend to react comparatively more slowly (> 10 h) than those possessing at least one aromatic substituent at the same positions (compare, for instance, **11k** with **11a** or **11n** with **11p**).[16] In line with this observation, substrates **10p–s**, which bear aromatic groups at both $C_{(2)}$ and $C_{(6)}$, exhibited the highest reactivity with conversions being complete in only 1 hour. Finally, it should be noted that substrates **10t** and **10u**, which have substituents at the propargylic position, were reacted as inseparable 1:1 mixtures of diastereoisomers. For **10t**, the two diastereoisomers, while leading to the formation of the same pyridine **11t**, were shown to react with different kinetics. One of the

Table 2: Substrate scope.[a]



[a] Substrate concentration: 0.1 M. Yields of isolated products. Reaction times are given in parentheses. [b] Based on the reacting diastereoisomer.

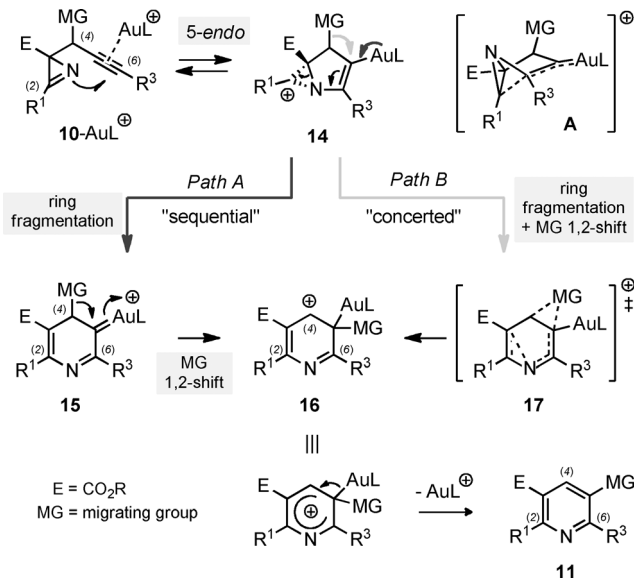
diasteroisomer completely reacted within 1 hour while 12 h were required for the other.[17] At the extreme limit, one of the diastereoisomers of **10u** did not react at all.[18] In the special case of substrate **10x** (Scheme 3), the two diastereoisomers $\mathbf{10x}_{syn}$ and $\mathbf{10x}_{anti}$ could be separated and their relative configurations were assigned by X-ray diffraction analysis of $\mathbf{10x}_{syn}$. This allowed us to more conveniently compare their reactivities and to study the influence of the propargylic susbtituent on the course of the reaction.



Scheme 3. Reactions of diastereoisomers $\mathbf{10x}_{syn}$ and $\mathbf{10x}_{anti}$.

A slow but selective reaction was observed in the case of diastereoisomer $\mathbf{10x}_{syn}$, which delivered the expected pyridine **11x** in 66% yield after 12 h of reaction (69% conversion).[17] The transformation of diastereoisomer $\mathbf{10x}_{anti}$ was more favorable and complete conversion was observed after 9 h. However, the reaction proved to be surprisingly unselective and another pyridine **11x′** was formed along with **11x** (72% global yield; **11x**/**11′x** = 1.8:1).[19] This difference in reactivity, with the unusual migration of the aromatic group from position $C_{(4)}$ in $\mathbf{10x}_{anti}$ to position $C_{(5)}$ in **11x′**, provides significant insights into the possible reaction mechanism and the reactive intermediates that could be involved.

A proposed general mechanism[20] for the formation of pyridines **11** from propargylic 2*H*-azirine derivatives **10** is given in Scheme 4. The transformation could be initiated by an electrophilic activation of the alkyne by the gold complex, which would induce the 5-*endo* nucleophilic addition of the azirine fragment. This would generate the aziridinium species **14**,[21] the formation of which should be favored in the presence of R^1 groups with the ability to stabilize the incipient positive charge. Some potential back-donation from gold may also help in stabilizing intermediate **14**, which would thus be better represented as species **A**. As proposed in our mechanistic design [Scheme 1, Eq. (4)], **14** would then evolve into an α-imino gold–carbene intermediate of type **15**[9] following a gold-assisted ring-fragmentation process (Path A). A subsequent 1,2-shift of a migrating group (MG; MG = H for **10a–w** or 3,4,5-$(MeO)_3$-C_5H_2 for $\mathbf{10x}_{anti}$) from position $C_{(4)}$ to $C_{(5)}$ would generate the charge-delocalized



Scheme 4. Proposed mechanism.

intermediate **16**, which would then ultimately evolve into pyridine **11** with regeneration of the gold catalyst.

However, this mechanism alone does not explain the different product selectivity obtained for the reactions of diastereoisomers $\mathbf{10x}_{syn}$ and $\mathbf{10x}_{anti}$ (Scheme 3). Following Path A, the same α-imino gold–carbene intermediate **15** should indeed be formed from $\mathbf{10x}_{syn}$ and $\mathbf{10x}_{anti}$, and identical results should therefore be obtained from both epimers. An alternative mechanistic scenario that accounts for our experimental observations can be envisaged.[22] Instead of being produced following a sequential reaction pathway, intermediate **16** could alternatively be the result of a more concerted process in which the ring fragmentation and the 1,2-shift proceed concomitantly via a transition state of type **17** (Path B). In such a scenario, one can easily conceive that, in the case of diastereoisomers $\mathbf{10x}_{syn}$ and $\mathbf{10x}_{anti}$, the difference in relative stereochemistry at $C_{(3)}$ and $C_{(4)}$ would directly impact the geometry of the corresponding intermediates **14** and therefore the energy levels of the transition states **17**, thus leading to the migration of either a hydrogen atom or a trimethoxyphenyl group from $C_{(4)}$ to $C_{(5)}$.

In conclusion, we have developed a new gold-catalyzed reaction that enables the formation of polysubstituted functionalized pyridines from easily accessible 2-propargyl 2*H*-azirine derivatives. This transformation, which corresponds to an unprecedented intramolecular transfer of an alkenyl nitrene to an alkyne, proceeds with low catalyst loading, is efficient, and exhibits a high functional-group tolerance and a wide substrate scope. Additional investigations aimed at clarifying the reaction mechanism, as well as further studies on the development of new metal-mediated processes involving 2*H*-azirines, are currently underway.

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[16] The possible coordination of the gold complex to the pyridine products, a process that should compete with the activation of the alkyne moiety, could explain in part why the transformation of substrates **10k–m** required longer reaction times. Such a coordination should indeed be more favorable in the case of the more basic 2,6-dialkyl substituted pyridines **11k–m**.
[17] For the less reactive diastereoisomer of **10t** and for **10x**$_{syn}$, the formation of the corresponding intermediate **14** (Scheme 4) should be disfavoured by a strong steric interaction arising from the *cis* relationship between the aromatic group at $C_{(4)}$ and the *tert*-butyl ester at $C_{(3)}$. This would account for the longer reaction time observed.
[18] The unreactive diastereoisomer of **10u** is probably that possessing the same relative stereochemistry to that found in **10x**$_{syn}$. The formation of the corresponding intermediate **14** (Scheme 4) should be disfavoured by a strong steric interaction arising from the *cis* relationship between the ethyl group at $C_{(4)}$ and the *tert*-butyl ester at $C_{(3)}$. The complete inertness of this diastereoisomer of **10u** when compared to **10x**$_{syn}$ can be explained by considering that an ethyl group would possess a lower capacity than an aromatic group to stabilize an incipient positive charge during a concerted process leading from **14** to **16** (Path B) and involving the migration of an hydrogen atom(MG=H).
[19] The electron-rich 3,4,5-trimethoxyphenyl group possesses a greater migratory aptitude than a simple phenyl group and can therefore compete with the hydrogen atom at $C_{(4)}$ for the 1,2-shift step, thus leading to **16** (Scheme 4).
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[22] Both mechanisms could operate since one does not exclude the other.

