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Very Important Publication

Construction of Enantioenriched 4,5,6,7-Tetrahydrofuro[2,3-*b*] pyridines through a Multicatalytic Sequence Merging Gold and Amine Catalysis

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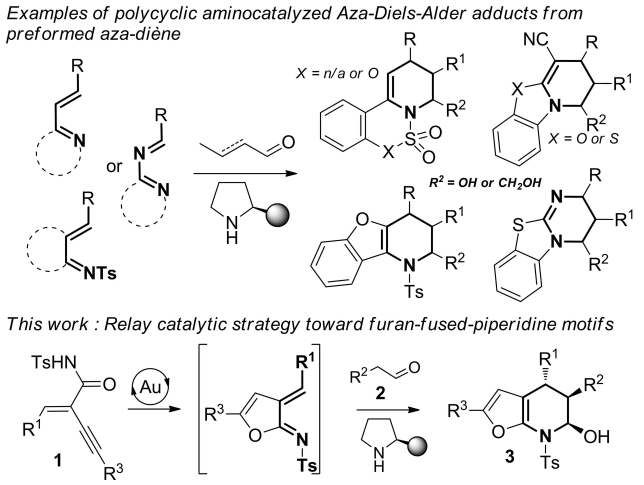
Abstract: A series of enantioenriched 4,5,6,7-tetrahydrofuro[2,3-*b*]pyridines were accessed by a cycloisomerization/cycloaddition strategy. Starting from ynamide derivatives and aldehydes, yields ranging from 27 to 90% and high levels of stereoselectivity (de > 95%, 93–99% ee) were obtained through sequential relay catalysis. The concurrent use of a gold complex with a diphenylprolinol silyl ether was applied to a combination of diversely functionalized substrates.

Keywords: Aminocatalysis; Gold catalysis; Relay catalysis; Aza-Diels-Alder; Saturated heterocycles

The asymmetric catalytic construction of N-saturated heterocycles continues to attract considerable attention because of the prevalence of these structural motifs in natural products or biologically active compounds and because sp^3-rich nitrogen scaffolds are among the most important structural components of pharmaceuticals.[1] Aza-Diels-Alder reaction (ADAR) illustrates perfectly this finding. Over the past decades, a myriad of elegant stereoselective methods promoted by a chiral catalyst have been reported thus highlighted the effectiveness of this transformation for the synthesis of useful nitrogen heterocycles.[2] Particularly in recent years, many research groups have exploited the ability of chiral organic molecules to activate diene and/or dienophile partners and allow normal or inverse electron-demand [4+2] cycloaddition to take place.[3] Among the different activations made possible by these promoters, aminocatalytic HOMO-raising strategies have successfully demonstrated the propensity of chiral secondary amines to activate carbonyl compounds as electron-rich dienes or dienophiles to undergo such transformation.[4] Illustrating the potential of such activation mode, Chen reported the first aminocatalytic asymmetric inverse-electron-demand Aza-Diels–Alder reaction of N-sulfonyl-1-aza-1,3-butadienes and aliphatic aldehydes.[5–6] The methodology has been further implemented in remote functionalization of α,ß-unsaturated carbonyls with the concomitant use of cyclic 1-azadiene.[7] Thus, preformed electron-poor heterodienes bearing cyclic sulfonamides, and sulfamidates,[8] benzoxazoles and benzothiazoles,[8a] benzothiazolimine[9] or aurone-derived azadienes[10] have been engaged in the organocatalyzed cycloaddition reaction giving rise to diverse nitrogen-containing polycyclic architectures (Scheme 1). Despite great advances, new methodologies emphasizing the generation of structural diversity and complexity have yet to be explored. In this context, the combination of different catalysts to achieve synthetic efficiency and stereoselectivity inaccessible by a single catalyst is a promising strategy to address this challenge.[11]

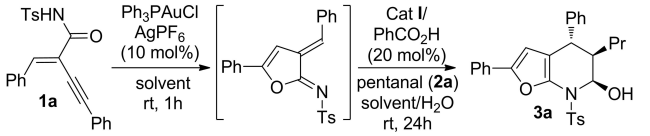
In this area, multicatalytic processes that merge the complementary activation offered by a metal and an organocatalyst have allowed the construction of enantioenriched complex structures from simple starting materials. In particular, cooperative (synergistic) or relay catalysis that employ the combination of an aminocatalyst with palladium, copper, iridium, ruthe-



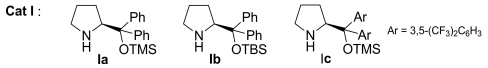
Scheme 1. Aminocatalytic HOMO-raising strategies toward polycyclic N-heterocycles.

nium, platinium or gold complexe have been used to synthesize functionalized enantioenriched cyclic motifs.[12] We described herein a relay catalytic strategy using the complementary activations of gold catalysis and aminocatalysis for the stereoselective formation of enantioenriched furan-fused tetrahydropyridine motifs. Very recent reports have shown that gold-catalyzed cycloisomerization of ynamides **1** could afford competent four-atom reaction partners that could be engaged in catalytic cyclization reactions.[13] We surmised that the transient azadiene formed during this catalytic event could be engaged in an aminocatalytic cycloaddition leading to the targeted skeletons. But we had to be mindful that a careful optimization of the reaction conditions ensuring the compatibility of the two catalytic steps was the key to the success of this tactic. We began our studies by investigating the gold and chiral amine sequential relay catalysis of ynamide **1a** and pentanal **2a** (Table 1). Cycloisomerization reaction of **1a** under gold(I) catalysis (Ph_3PAuCl/$AgPF_6$, 10 mol%) in dichloroethane (DCE) at room for 1 h led to the formation of electron-poor azadiene. Successive additions of the diarylprolinol silyl ether **Ia**[14] with an equal amount of benzoic acid (20 mol%) and pentanal **2a** enable the ADAR to proceed. In this case, the expected bicyclic compound **3a** was obtained in 25% yield and 80% ee (entry 1).[15] The influence of the aminocatalyst structure on the reaction was first investigated by using the catalyst **Ib** possessing a bulkier silyl group (e.g., TBS) and the 3,5-$(CF_3)_2C_6H_3$ derived catalyst **Ic** (entries 2 and 3). Both catalysts **Ib** and **Ic** resulted in a decrease of yields and enantioselectivities. We then examined the influence of the solvent on the ADAR by exploiting the concept of „pot-economy“ disclosed by Clarke[16] and developed by Hayashi.[17] This strategy consists in an “uninterrupted sequence of reactions” where only the removal

Table 1. Optimization of the reaction conditions.



entry	cat	solvent	H_2O (mL)	yield (%)[b]	ee (%)[c]
1	Ia	DCE	–	25	80
2	Ib	DCE	–	10	50
3	Ic	DCE	–	8	n.d.
4[d]	Ia	DCE then PhMe	–	41	98
5[d]	Ia	DCE then PhMe	0.1	45	99
6[d]	Ia	DCE then PhMe	0.2	35	99
7[d]	Ia	DCE then PhMe	0.05	63	99
8[d]	Ia	DCE then PhMe	0.025	74	99
9	Ia	PhMe	0.025	68	99
10[e]	Ia	DCE:PhMe (1:1)	0.025	52	98
12[f]	Ia	DCE:PhMe (1:4)	0.025	63	99



[a] Reactions were performed with **1a** (0.1 mmol), Ph_3PAuCl/$AgPF_6$ (10 mol%) in solvent (1 mL) at rt for 1 h then Cat **I**/$PhCO_2H$ (20 mol%), pentanal (0.15 mmol) and H_2O were added.
[b] Isolated yields.
[c] Determined by HPLC on a chiral stationary phase.
[d] DCE was evaporated after the 1st catalytic step and replace by PhMe (1 mL).
[e] DCE/PhMe (1 mL/1 mL).
[f] DCE/PhMe (0.25 mL/1 mL).

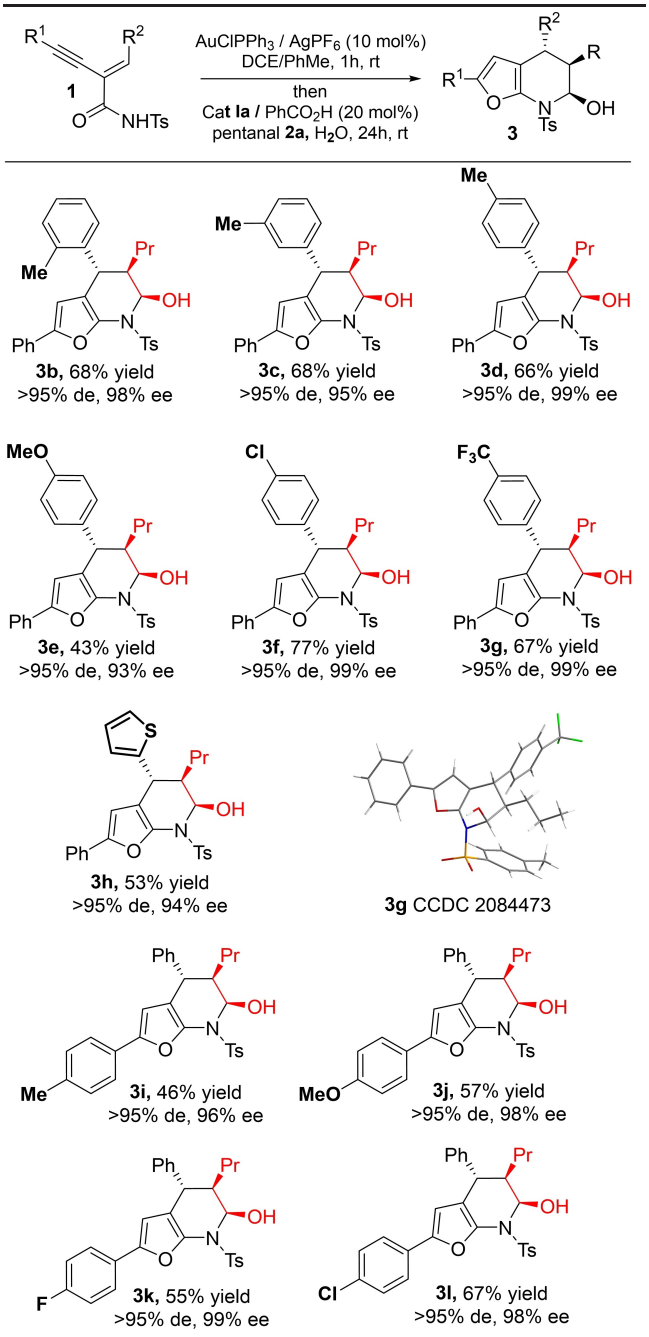
of volatiles from the reaction vessel by distillation is allowed. Following this principle, the conditions of the cycloisomerization step remained identical and DCE was evaporated after 1 h and replace by PhMe. Cat **Ia**, $PhCO_2H$, pentanal **2a** were then added and the reaction mixture was stirred 24 h (entry 4). In this case better yield (40%) and enantioselectivity (98%) were observed. As pointed out by Chen,[5] H_2O plays a pivotal role in this cycloaddition reaction and facilitate the catalytic turnover. Indeed, addition of different amount of water in the sequence (entries 5–8) resulted a significant increase of yield (best conditions: $V(H_2O) = 0.025$ mL, 74% yield, entry 8) affording **3a** with an excellent enantioselectivity (99% ee).

We were finally interested in setting up compatible solvent conditions for the whole multicatalytic process (entries 9–11). When PhMe (entry 9) or a mixture DCE:PhMe (1:4) (entry 11) was used as solvent from the outset of the transformation, only a slight decrease in term of yield was observed (68 and 63% respectively) but the high level of enantioselectivity was maintained (99% ee). Finally, due to solubility problem

encountered during the evaluation of the scope, the optimal condition to synthetize compounds **3** were selected as follow: ynamide **1** (0.1 mmol), Ph_3PAuCl/$AgPF_6$ (10 mol%) in a mixture DCE/PhMe (0.25 mL/0.5 mL) at rt for 1 h then a solution of cat. **Ia**/$PhCO_2H$ (20 mol%) in PhMe (0.5 mL), pentanal (0.15 mmol) and H_2O (25 µL) were added and the reaction mixture was stirred at room temperature for 24 h. Having established the best conditions, the scope of the transformation regarding to the substituants (R^2 group) bore by ynamide **1** was explored (Table 2). We initially focused on the reactivity of α,β-unsaturated ynamide **1b–1g** decorated with a substituted aromatic ring on the benzylidene moiety. In all cases, bicyclic scaffolds **3** were obtained with a high level of diastereoselectivity (>95% de). Regardless of the position (*ortho*, *meta*, *para*-position), the introduction of a methyl group did not influence the reaction outcome and bicyclic compounds **3b–3d** were isolated with similar levels of yields and enantioselection as **3a**. A decrease of yield and enantiomeric excess was observed on reacting **1e** bearing a *para*-methoxy substituent with **2a** In this case, **3e** was obtained in 43% yield and 93% ee. Ynamides **1f** and **1g** bearing respectively a chlorine atom or a trifluoromethyl group at the *para*-position of the aromatic ring were also amenable to the cycloisomerization/ADAR sequence by providing compounds **3f** or **3g** in good yields and 99% ee. The structure and the relative configuration of **3g** was unambiguously confirmed by single-crystal X-ray crystallography.[18] The thiophene-derived-amide **1h** was found to undergo a clean reaction to provide product **3h** with 53% yield and 94% ee. Unfortunately, no reaction took place when ynamide **1** bearing a strong electron withdrawing group (R^2 = 4-NO_2–C_6H_4) or 1-naphthyl substituent was engaged in the sequence. Variations to the alkyne moiety (R^1 group) were next investigated. Aromatic substituents decorated with either a methyl, a methoxy-group or halogen atoms (F, Cl) at the *para*-position are well tolerated, giving rise to the target products **3i-3l** in yields ranging from 46% to 68% and excellent enantiomeric excesses (>96% ee).

We then found that a variety of substituted aldehydes **2** are also amenable to the transformation with ynamide **1a** provided functionalized fused furans **3** in moderate to excellent yields and a high level of stereochemical induction was observed in each case (>95% de, >97% *ee*, Table 3). Not surprisingly, aliphatic aldehydes such as propanal, 3-phenylpropanal or 4-phenylbutanal were well tolerated leading respectively to **3m**, **3n** and **3o** in good yields. More interestingly, functionalized aldehydes can also efficiently participate in this reaction. Bicyclic skeleton **3p** bearing an alkyl chain decorated with and α,ß-unsaturated ester was formed in 60% yield. The reaction of *O*-protected α- or ß-hydroxy aldehydes afforded bicyclic skeletons **3q** and **3r** in 27% and 69% yield. Similar result was obtained for compound **3s**

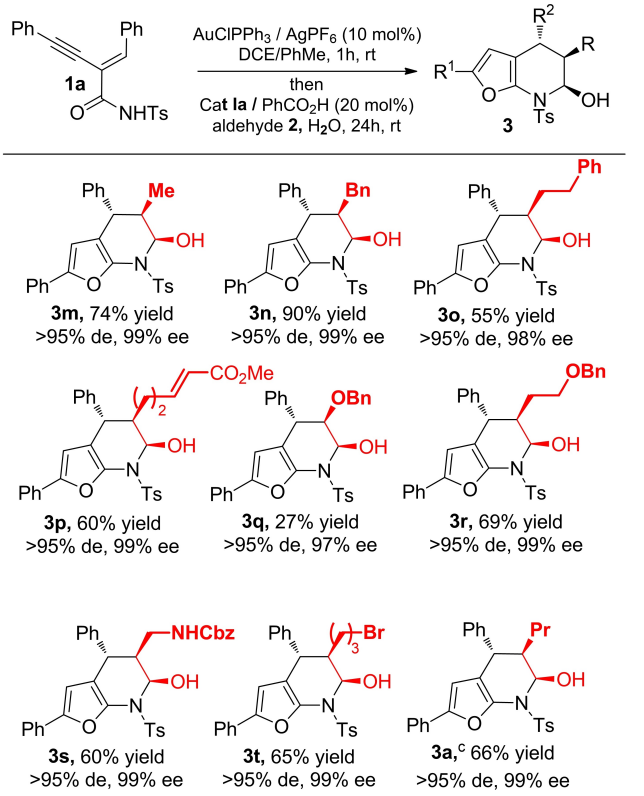
Table 2. Substrate scope of the amides **1**.[a,b]



[a] Reactions were performed with **1** (0.1 mmol), Ph_3PAuCl/$AgPF_6$ (10 mol%) in a mixture DCE/PhMe (0.25 mL/0.5 mL) at rt for 1 h then cat **Ia**/$PhCO_2H$ (20 mol%), pentanal (0.15 mmol), H_2O (25 µL) and PhMe (0.5 mL) were added.

[b] Yield refers to isolated yields after purification, diastereomeric excesses (de) were determined by ^1H NMR analysis of the crude and enantiomeric excesses (ee) were determined by HPLC on a chiral stationary phase.

Table 3. Substrate scope of the aldehydes **2**.[a,b]

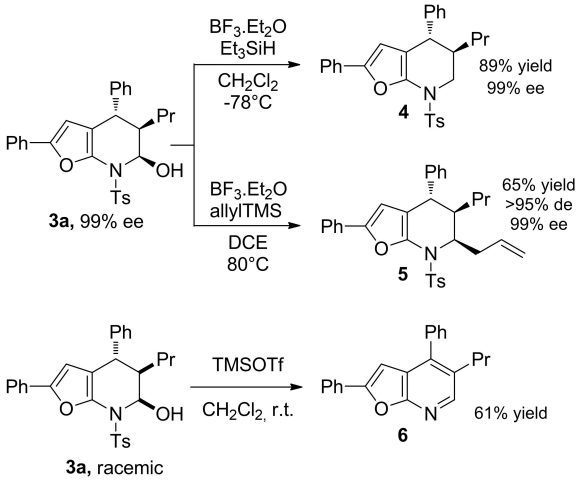


[a] Reactions were performed with 1a (0.1 mmol), Ph_3PAuCl/$AgPF_6$ (10 mol%) in a mixture DCE/PhMe (0.25 mL/0.5 mL) at rt for 1 h then cat Ia/$PhCO_2H$ (20 mol%), aldehyde 2 (0.15 mmol), H_2O (25 µL) and PhMe (0.5 mL) were added.

[b] Yield refers to isolated yields after purification, diastereomeric excesses (de) were determined by ^1H NMR analysis of the crude and enantiomeric excesses (ee) were determined by HPLC on a chiral stationary phase.

[c] Reaction performed on 1 mmol scale.

starting from *N*-protected ß-amino aldehyde. A bromide-substituted chain was also a suitable substrate for this sequence and provided **3t** in 65% yield. Finally, we demonstrate that the sequential relay catalysis of ynamide **1a** and pentanal **2a** still proceeded smoothly when performed on 1 mmol scale. To further increase the functional-group diversity of our compounds, transformations of compound **3** into chiral tetrahydropyridine motifs **4** and **5** were carried out (Scheme 2). Compound **3a** was stirred in the presence of $BF_3.Et_2O$ and triethylsilane to yield 4 in 89% yield. Moving from a silicon-based reducing agent to trimethylallylsilane allowed the formation of more substituted tetrahydropyridine ring **5** bearing three continuous stereocentres. Finally, the construction of biologically valuable furo[3,2-b]pyridines[19] from **3a** was considered. A racemic mixture of **3a** was engaged in an oxidative transformation in the presence



Scheme 2. Synthetic transformations.

of trimethylsilyl trifluoromethanesulfonate (1 equiv.) to afford furo[3,2-*b*]pyridine 6 in 61% yield.

In summary, we have developed a sequential relay catalytic transformation leading to enantioenriched functionalized polycyclic N-heterocycles **3**. A combination of $Ph_3PAuCl/AgPF_6$ with OTMS-prolinol Ia catalyst turned out to be the best catalytic system to trigger the gold-catalyzed cycloisomerization/amino-catalytic cycloaddition sequence. Yields between 27 and 90% and high levels of stereoselectivity (*de* > 95% and *ee* from 93 to 99%) were observed for a range of ynamides and aldehydes involved in the transformation.

Experimental Section

General Procedure for the Synthesis Tetrahydro Furo[3,2-*b*]pyridines 3

In a dried and nitrogen filled Schlenk flask, a mixture of PPh_3AuCl (5.0 mg, 0.01 mmol, 10 mol%), $AgPF_6$ (2.5 mg, 0.01 mmol, 10 mol%) in DCE (0.25 mL) was stirred at room temperature under nitrogen for 30 min to generate the gold catalyst. Ynamide **1** (0.1 mmol) and toluene (0.5 mL) were added to the above catalyst solution under nitrogen. The resulting mixture was stirred for 1 h. A solution of organocatalyst **Ia** (6.5 mg, 0.02 mmol, 20 mol%) in toluene (0.5 mL), benzoic acid (2.1 mg, 0.02 mmol, 20 mol%), aldehyde **2** (0.15 mmol) and H_20 (25 µL) were added. The resulting mixture was stirred 24 h at room temperature and concentrated under reduced pressure to afford the crude product. Preparative TLC purification (pentane/EtOAc) afforded the desired product **3**.

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