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Asymmetric One-Pot Sequential Organo- and Gold Catalysis for the Enantioselective Synthesis of Dihydropyrrole Derivatives

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Abstract: A direct asymmetric one-pot synthesis of optically active 2,3-dihydropyrroles from propargylated malononitrile and *N*-Boc-protected (Boc = *tert*-butoxycarbonyl) imines is presented. The approach is based on a bifunctional organocatalytic Mannich-type reaction and a subsequent gold-catalyzed alkyne hydroamination and isomerization. The compatibility of both catalytic systems is presented and the overall transformation results in good yields (up to 70%) with high selectivities (*endo*/*exo* > 10:1) and enantioselectivities (up to 88% *ee*). The absolute configuration of the final products is unambiguously established by X-ray analysis. To highlight the synthetic potential of the accessed heterocyclic compounds, their transformation into 1-pyrrolines, which represent direct precursors of pyrrolidines, is presented.

Keywords: asymmetric catalysis · bifunctional thioureas · gold · one-pot processes · organocatalysis

Introduction

Optically active 2,3-dihydropyrroles are important unsaturated heterocyclic compounds applied as synthetic building blocks, potential therapeutic leads, and materials in modern chemistry. In addition, pyrrole derivatives can be transformed into multisubstituted pyrrolidines, serve as templates for the design of new organocatalysts and also be applied to the total synthesis of natural products.[1] Despite their numerous applications, the asymmetric catalytic synthesis of optically active 2,3-dihydropyrroles remains limited to, for example, metal-catalyzed partial hydrogenations of 2,3,5-trisubstituted pyrroles[2] and organocatalytic formal [3+2] cycloaddition reactions of isocyanoesters with nitroolefins.[3]

The need and interest for practically simple and synthetically efficient organic transformations has led to the development of many innovative strategies, concepts, and methodologies. The idea of combining transition-metal catalysis[4] with organocatalysis[5] in a multicatalytic fashion has emerged as a promising strategy in asymmetric synthesis, allowing access to new chemical reactivities and high molecular complexity from simple starting materials, or unexplored combinations of reactants.[6] Consequently, the combination of efficient catalytic methods in a tandem[7] or one-pot process[8] could provide a powerful tool for preserving both energy and resources.[9] To this end a multicatalytic asymmetric cascade reaction to cyclopentene carbaldehydes from α,β-unsaturated aldehydes and alkyne-tethered nucleophiles employing a combination of iminium–enamine and Lewis acid catalysis was recently reported.[7c–e] Furthermore, Alexakis and co-workers have described a one-pot process consisting of an enantioselective organocatalytic Michael addition to nitroenynes and a subsequent gold-catalyzed acetalization/cyclization for the synthesis of nitro-substituted tetrahydrofuranyl ethers.[8a]

In continuation of our research in combining organocatalysis with other chemical concepts,[10] and inspired by the work of Dixon et al.[11] who presented a cascade reaction to access racemic 2-methylenepyrrolidines from protected imines and propargylated malonates using base and copper(I) catalysis; we now report a novel approach to highly functionalized optically active 2,3,3,5-tetrasubstituted 2,3-dihydro-1*H*-pyrroles from imines and propargylated pronucleophiles (Scheme 1).

Results and Discussion

We started our investigations by reducing the operational complexity of the strategy presented in Scheme 1 by divid-

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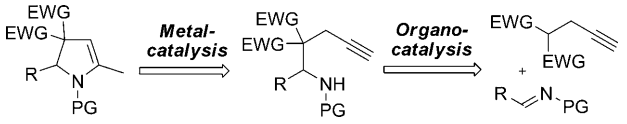
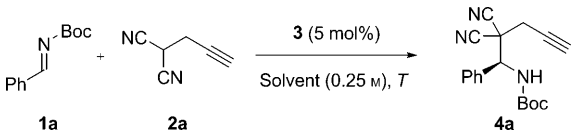


Scheme 1. Novel approach towards optically active 2,3,3,5-tetrasubstituted 2,3-dihydro-1*H*-pyrroles.

ing it into two separate assignments: the initial studies focus on the introduction of enantioselectivity, whereas the second concentrate on the cyclization protocol.

Enantioselective organocatalytic Mannich reaction: Initially, we examined the organocatalytic Mannich reaction of *N*-Boc-protected imine **1a** (Boc = *tert*-butoxycarbonyl) with propargylated malononitrile **2a** providing the enantioenriched key intermediate **4a** (Table 1). Previous studies have

Table 1. Screening of catalysts for the enantioselective addition of **2a** to **1a**.

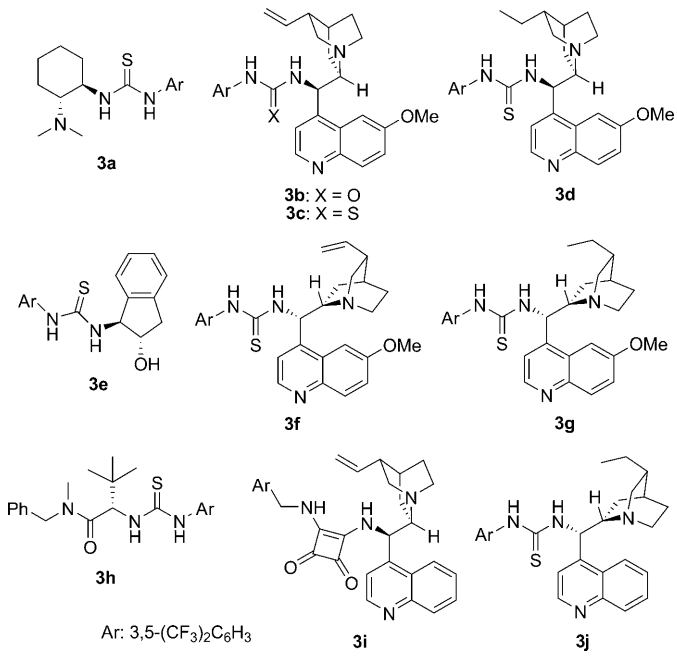


1a **2a** **4a**

Entry	Cat.	Solvent	T [°C]	Conv.[b] [%]	ee[c] [%]
1	–	$CDCl_3$	RT	5	–
2	Et_3N	CH_2Cl_2	RT	>95	–
3	**3a**	toluene	RT	>95	10
4	**3a**	toluene	−25	>95	16
5	**3b**	toluene	−25	>95	5
6	**3c**	toluene	−25	>95	48
7	**3d**	toluene	−25	>95	28
8	**3e**	toluene	RT	80	10
9	**3e**	toluene	−25	nr[d]	–
10	**3f**	toluene	−25	>95	−34
11	**3g**	toluene	−25	>95	−32
12	**3h**	toluene	−25	nr	–
13	**3h**[e]	toluene	−25	>95	*rac*
14	**3i**	toluene	−25	>95	10
15	**3j**	toluene	−25	>95	−30

[a] All the reactions were performed using **1a** (0.15 mmol), **2a** (0.10 mmol), and cat. (5 mol%). [b] Determined by ^{1}H NMR spectroscopy (after 20 h). [c] Determined by chiral stationary-phase HPLC. [d] nr = no reaction. [e] Employing NaOAc (0.5 equiv) as additive.

shown that bifunctional thiourea–amine organocatalysts are effective promoters for activation of pronucleophiles and *N*-Boc-protected imines through acid–base interactions.[12] Therefore, we performed an extensive investigation of several bifunctional catalysts (Scheme 2) and the results of the screening are presented in Table 1. The first control experiment was performed without any catalyst to examine the background reaction, which gave only 5% conversion as detected by ^{1}H NMR spectroscopy (Table 1, entry 1). Using 5 mol% of Et_3N, the adduct **4a** was obtained with full conversion, providing easy access to *rac*-**4a**. Preliminary results showed that imine **1a** might be effectively activated by hydrogen bonding at RT (Table 1, entries 3 and 8), albeit with



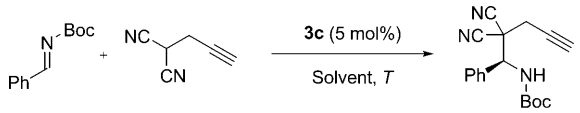
Scheme 2. Selection of screened catalysts for the Mannich reaction.

low enantiomeric excess (10% *ee*). Bifunctional urea, thiourea, and squaramide organocatalysts afforded good conversions at −25 °C (Table 1, entries 4–7 and 9–15).

These preliminary results revealed catalyst **3c**, derived from quinidine,[13] as the most promising scaffold providing **4a** with full conversion and 48% *ee* (Table 1, entry 6). Similar reactivities were observed for catalysts **3f**, **3g**, and **3j**, although lower enantioselectivities of *ent*-**4a** were obtained (Table 1, entries 10, 11, and 15). In contrast, urea-derived **3b** and squaramide (**3i**), provided poor enantioselectivities in the model reaction (Table 1, entries 5 and 14), which suggested that a thiourea functionality is essential for stereocontrol. Interestingly, different alkyne-tethered nucleophiles **2** derived from malonates or 1,3-diketones showed no reactivity and the differently protected *N*-*p*-toluenesulfonyl and *N*-*p*-methoxyphenyl imines afforded the Mannich products **4** in low yields and enantioselectivities. Substituting the *N*-Boc with analogous *N*-benzoyl imines provided the corresponding products **4** in good yields, albeit in slightly lower enantioselectivities.

Having confirmed **3c** as the most promising catalyst, a survey of the reaction parameters (solvent, temperature, and concentration) was performed as outlined in Table 2. Excellent reactivity and moderate enantioselectivity were obtained in toluene (Table 2, entry 1); however, increased enantioselectivity was observed by employing halogenated solvents such as CH_2Cl_2 or $CHCl_3$, giving the product **4a** in 66 and 70% *ee*, respectively (Table 2, entries 7 and 8). Conducting the reaction in dioxane, THF, or hexane[14] had a detrimental effect on the reactivity and enantioselectivity of the reaction giving **4a** with up to 50% conversion (after 22 h) and poor enantioselectivities (Table 2, entries 2, 3, and 5). Interestingly, other polar aprotic solvents like CH_3CN

Table 2. Optimization for the enantioselective addition of **2a** to **1a** catalyzed by **3c**.



1a **2a** **4a**

Entry	**3c** [mol %]	[**2a**] [M]	Solvent	T [°C]	Conv.[b] [%]	*ee*[c] [%]
1	5	0.25	toluene	−25	>95	48
2	5	0.25	dioxane	RT	40	10
3	5	0.25	THF	−25	50	*rac*
4	5	0.25	CH_3CN	−25	>95	−16
5	5	0.25	hexane	−25	50	−13
6	5	0.25	acetone	−25	>95	−16
7	5	0.25	CH_2Cl_2	−25	>95	66
8	5	0.25	$CHCl_3$	−25	>95	70
9	5	0.05	$CHCl_3$	−25	>95	78
10	2	0.05	$CHCl_3$	−60	>95	82
11	1	0.05	$CHCl_3$	−60	>95	82
12[d]	1	0.05	$CHCl_3$	−60	50	82
13[e]	1	0.05	$CHCl_3$	−60	nr	–

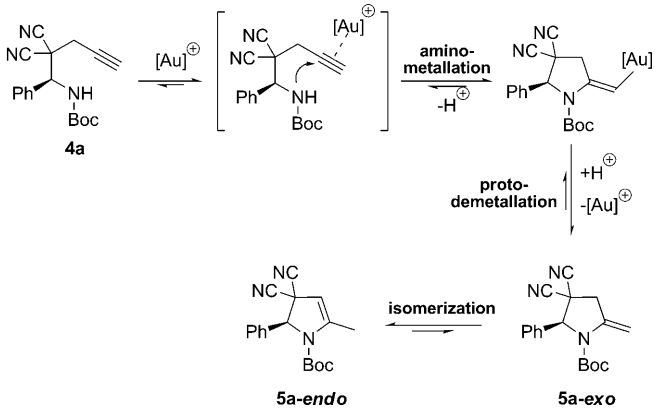
[a] All the reactions were performed using **1a** (0.15 mmol), **2a** (0.10 mmol), and **3c** and were stirred for 22 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary-phase HPLC. [d] 1 mol % of TFA as additive. [e] 2 mol % of TFA as additive.

and acetone afforded full conversions to *ent*-**4a**, albeit with lower enantioselectivity (Table 2, entries 4 and 6). This stereochemical reversal may be indicative of a change in operation pathway of the catalyst. Self-association of the cinchona-alkaloid derived thiourea catalysts as noncovalent dimers in solution has been observed.[15] Equilibria between mono- and dimeric species, in different solvents, can give different stereochemical outcomes.

Dilution of the reaction mixture ([**2a**] = 0.05 M) increased the enantioselectivity, providing **4a** in 78 % *ee* (Table 2, entry 9). Under these conditions, lowering the catalyst loading to 1 mol % and decreasing the reaction temperature to −60 °C provided an increased selectivity of 82 % *ee* (Table 2, entry 11). Similar observations have been made in other studies using this class of catalysts.[16] Finally, the influence of cocatalysts in the reaction was investigated by employing trifluoroacetic acid (TFA) as an additive. The addition of 1 mol % of TFA led to a slower reaction and no influence on the enantioselectivity was found (Table 2, entry 12). Increasing the amount of TFA to 2 mol % deactivated catalyst **3c** (Table 2, entry 13), indicating the importance of the basic functional group(s) in the catalyst.

We propose that the imine is activated by the thiourea moiety through hydrogen bonding and the nucleophile is concurrently activated through base-catalysis by one of the basic sites in the catalyst.

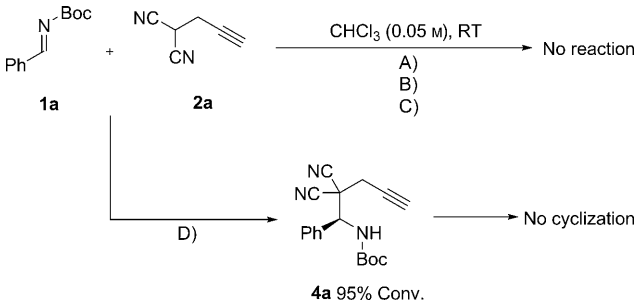
Intramolecular metal-catalyzed alkyne hydroamination: In the next stage of our studies, the intramolecular metal-catalyzed alkyne hydroamination[17] of intermediate **4a** into the corresponding *tert*-butyl 3,3-dicyano-5-methyl-2-phenyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate (**5a**) (Scheme 3) in the presence of various metal sources and additives was investigated. Surprisingly, a series of metal salts (Cu, Ag, Pd, Ni, Rh, Fe, Pt, Zn, or In salts) described for this type of transformation were inactive in the present system (see the Supporting Information). However, we were pleased to find that activation of the triple bond by AuCl or $AuCl_3$[18] salts afforded **5a** in 80 % conversion (after 22 h) with high selectivity (*endo*/*exo* 9:1) referring to the positional isomerism of the double bond.



Scheme 3. Gold-catalyzed intramolecular alkyne hydroamination of **4a**.

Gold catalysts are well known for activating alkynes by forming π-complexes. The triple bond of **4a** is activated towards the attack by the nitrogen atom in a 5-*exo*-*dig* fashion as outlined in Scheme 3, and subsequent protodemetallation affords the 2-methylenepyrrolidine kinetic product **5a**-*exo*, followed by alkene isomerization to **5a**-*endo* (see below).

One-pot bifunctional organocatalytic Mannich, gold-catalyzed alkyne hydroamination cascade: Having optimized the enantioselective organocatalytic Mannich addition of **2a** to **1a** and identified Au^I- or Au^{III}-salts as suitable Lewis acids for intramolecular alkyne hydroamination of adduct **4a**, we then examined the combination of both catalytic reactions providing the 2,3-dihydropyrrole derivative **5a** in a multicatalytic cascade process (Scheme 4). Preliminary experiments combining thiourea and gold catalysis were unsuccessful, since organocatalyst **3c** and Au-salts exhibit strong affinities for each other, as observed by ^{31}P NMR spectroscopy. Indeed, depending on the ratio of **3c**/[Au] employed simul-



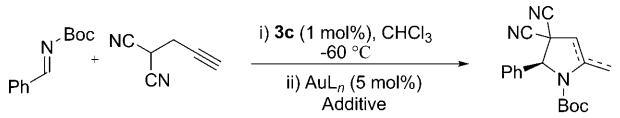
1a **2a** **4a** 95% Conv.

Scheme 4. Preliminary experiments combining **3c** and Au salts in a cascade process. Conditions: A) **3c** (1 mol %)/[Au] (5 mol %); B) **3c** (3 mol %)/[Au] (5 mol %); C) **3c** (5 mol %)/[Au] (5 mol %); D) **3c** (10 mol %)/[Au] (5 mol %).

taneously, different results were obtained. Employing excess or equimolar amounts of gold to **3c** led to inhibition of the Mannich reaction (Scheme 4, conditions A–C). When an excess of thiourea was employed (**3c**/[Au], 2:1), intermediate **4a** was formed in >95% conversion (Scheme 4, condition D). Unfortunately, employing this reaction condition resulted in deactivation of the Au complex for the subsequent alkyne hydroamination.

Therefore, taking into consideration the proved inactivation of thiourea **3c** in the presence of Au salts for the initial Mannich reaction, we decided to investigate the possibility of accomplishing both catalytic reactions in a sequential one-pot procedure (Table 3). Then, the organocatalytic Mannich reaction was performed employing the optimized

Table 3. Optimization of the one-pot synthesis of 2,3,3,5-tetrasubstituted 2,3-dihydropyrrole **5a**.



1a **2a** **5a**-(*endo* + *exo*)

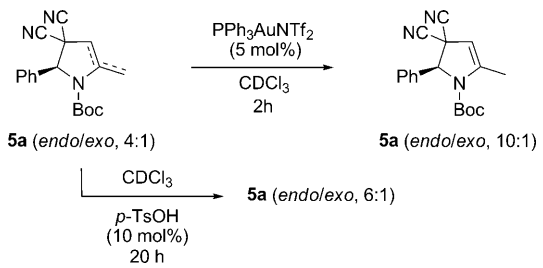
Entry	AuL_n	Additive (%)	t[b] [h]	Conv.[c] [%]	*endo*/*exo*[c]
1	AuCl	–	22	70	2:1
2	$AuCl_3$	AgOTf (15)	22	70	2:1
3	PPh_3AuCl	AgOTf (5)	9	>95	3:1
4	PPh_3AuNTf_2	–	9	>95 (76)[d]	3:1
5	PPh_3AuNTf_2	EtOH (500)	9	>95 (30)[d]	8:1
6	PPh_3AuNTf_2	$PhCO_2H$ (20)	6	>95 (60)[d]	9:1
7	PPh_3AuNTf_2	*p*-TsOH (10)	4	>95 (70)[d]	>10:1
8	–	*p*-TsOH (10)	22	nr	–
9	PPh_3AuNTf_2	proton sponge (20)	22	nr	–

[a] All the reactions were carried out on a 0.1 mmol scale (0.05 M) using **1a** (0.15 mmol), **2a** (0.10 mmol), and **3c** (0.001 mmol). [b] Reaction time for the second step. [c] Determined by ^1H NMR spectroscopy. [d] Yield of the isolated product.

conditions (**3c** (1 mol%), $CHCl_3$ [0.05 M], −60 °C) and upon completion of the reaction (22 h), an excess amount of $AuCl_n$ (5 mol%) was added at room temperature affording **5a** in 70% conversion after 22 h (Table 3, entries 1 and 2). Surprisingly, we observed a decrease of the selectivity, with respect to the constitutional isomers, in the one-pot procedure (*endo*/*exo* 2:1, Table 3, entries 1 and 2), compared with the two-step reaction (*endo*/*exo* 9:1, see the Supporting Information). Further optimization of the cyclization step was performed by using different gold catalysts and additives. Cationic Au^I complexes showed higher reactivities, leading to full conversions in shorter reaction times (Table 3, entries 3 and 4). Performing the reaction in the presence of EtOH (5 equiv), provided **5a** with good selectivity (*endo*/*exo* 8:1), albeit in lower yield (Table 3, entry 5). The best results were obtained using PPh_3AuNTf_2 in combination with acidic additives (Table 3, entries 6 and 7). A catalyst **3c**/PPh_3AuNTf_2/*p*-TsOH ratio of 1:5:10 proved to be the optimum conditions forming **5a** in good yield (70%) and selectivity (*endo*/*exo* >10:1, Table 3, entry 7). A control experiment employing *p*-TsOH (10 mol%) in the absence of a gold salt was performed to rule out the possibility of acid-catalyzed hydroamination[19] of **4a** (Table 3, entry 8).

We also observed a dramatic effect when using bases as additives in terms of reactivity, from no reaction in the presence of a proton sponge (DMAN) (Table 3, entry 9) to decomposition by a retro-Mannich reaction when applying stronger bases, such as KO*t*Bu. These investigations demonstrate that additives have a tremendous effect on the outcome of the reaction. Acidic cocatalysts increase the reactivity and selectivity (*endo*/*exo*) of the process.

To shed light over the isomerization step, control experiments were conducted in $CDCl_3$. As outlined in Scheme 5, ^1H NMR spectroscopic monitoring of a mixture of **5a** (*endo*/*exo* 4:1) in the presence of *p*-TsOH (10 mol%) ruled out a rapid Brønsted acid catalyzed alkene isomerization (**5a** *endo*/*exo* 6:1 after 20 h). However, PPh_3AuNTf_2 promoted the isomerization[20] in the standard reaction time scale (**5a** *endo*/*exo* 7:1 after 30 min, 10:1 after 2 h). Therefore, it is believed that excess *p*-TsOH prevents deactivation of the Au^I-catalyst by protonating the basic quinuclidine and quinoline moieties of **3c**.[21]

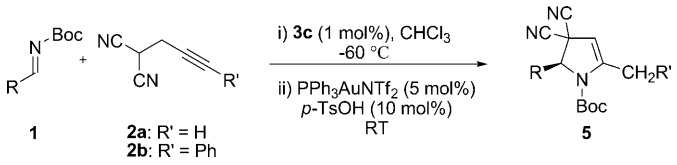


Scheme 5. Gold-catalyzed alkene isomerization.

Scope of the one-pot synthesis of optically active 2,3-dihydro-1*H*-pyrroles: Having developed an efficient one-pot protocol for the synthesis of 2,3,3,5-tetrasubstituted 2,3-dihydropyrroles **5**, the generality of the reaction was studied for a series of *N*-Boc-protected imines (Table 4).

Employing alkyl-substituted aromatic imines **1b**–**1d** showed that the outcome of the reactions was reasonably independent of aromatic substitution pattern (Table 4, entries 2–4) and the optically active 2,3-dihydropyrroles **5b**–**5d** were formed in good yields (60–65%) and enantioselectivities (82–88% *ee*). The naphthyl-based imine **1e** gave rise to the heterocycle **5e** (Table 4, entry 5) in 65% yield and 72% *ee*. Importantly, electron-poor aromatic imines **1f** and **1g** can also be employed (Table 4, entries 6 and 7) affording the corresponding 2,3-dihydropyrroles **5f** and **5g** in good yields (74–80%) and enantioselectivities (68–72% *ee*). However, the more electron-rich *p*-methoxy phenylimine **1h** and heteroaromatic thiophene-based imine **1i** gave the desired products **5h** and **5i** (Table 4, entries 8 and 9) in good yields (45–70%), albeit in moderate enantioselectivities (58% *ee*).

Table 4. Scope of the one-pot synthesis of optically active 2,3-dihydro-1*H*-pyrroles.



Entry	R	2	Product	Yield[b] [%]	*ee*[c] [%]
1	Ph **1a**	**2a**	**5a**	70	82
2	*o*-Me-Ph **1b**	**2a**	**5b**	65	84
3	*m*-Me-Ph **1c**	**2a**	**5c**	60	82
4	*p*-Me-Ph **1d**	**2a**	**5d**	60	88
5	1-napthyl **1e**	**2a**	**5e**	65	72
6	*p*-Cl-Ph **1f**	**2a**	**5f**	80	72
7	*p*-Br-Ph **1g**	**2a**	**5g**	74	68
8	*p*-MeO-Ph **1h**	**2a**	**5h**	45	58
9	2-thienyl **1i**	**2a**	**5i**	70	58
10[d]	Ph **1a**	**2b**	**4b**	93	78

[a] All the reactions performed on a 0.1 mmol scale (see the Supporting Information). [b] Isolated by flash chromatography. [c] Determined by chiral stationary-phase HPLC. [d] Employing **3c** (5 mol%), **4b**: Mannich adduct.

It should be noted that excellent selectivities (*endo*/*exo* > 10:1) were obtained in all cases.

We then investigated the possibility of incorporating a phenyl group attached to the terminal alkyne as this newly designed 2-(3-phenylprop-2-ynyl)malononitrile (**2b**) would provide arylbenzyldihydropyrroles. Under standard organocatalytic conditions, the Mannich adduct **4b** was obtained in 93% yield and 78% *ee* (Table 4, entry 10). Unfortunately, no cyclization was observed by employing various conditions.[22]

Absolute configuration and synthesis of optically active 2,3,3,5-tetrasubstituted 1-pyrrolines: The absolute configuration of **5i** was assigned to be (*R*) by X-ray analysis as shown in Figure 1.[23] The absolute configurations of the products

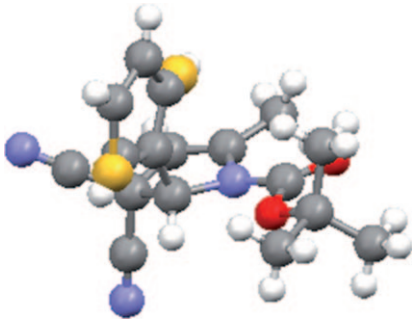
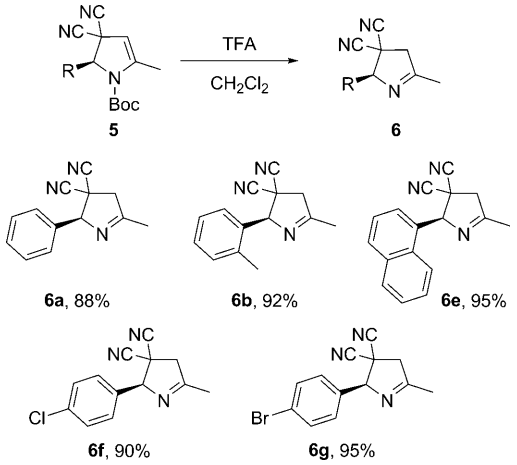


Figure 1. X-ray crystal structure of compound **5i** (C gray, H white, O red, N blue, S yellow).

4–**6** were assigned by assuming a uniform reaction pathway by which the nucleophile **2** adds to the *Re* face of the imine **1**.

To highlight the synthetic potential of the products **5**, their simple transformation into 1-pyrrolines **6**, direct precursors of pyrrolidines,[24] is presented in Scheme 6. Treating



Scheme 6. Transformation of dihydropyrroles **5** into optically active 2,3,3,5-tetrasubstituted 1-pyrrolines **6**.

optically active dihydropyrroles **5** with TFA in CH_2Cl_2 afforded 1-pyrrolines **6** in good yields (88–95%) without the need for elaborate purifications, such as flash chromatography.

Conclusion

We have reported a novel synthetic approach towards optically active 2,3,3,5-tetrasubstituted 2,3-dihydro-1*H*-pyrroles **5**. The protocol involves a combination of bifunctional thiourea organocatalysis and gold catalysis in a one-pot sequential fashion. In the alkyne hydroamination, thiourea-based hydrogen bonding organocatalyst **3c** and gold-based Lewis acid PPh_3AuNTf_2 proved to be compatible upon protonation by *p*-TsOH. The obtained highly functionalized heterocycles **5** may serve as templates for the design of new organocatalysts or natural product synthesis. The synthetic potential of optically active 2,3-dihydro-1*H*-pyrroles **5** has been illustrated by a simple transformation into 1-pyrrolines **6**, direct precursors of pyrrolidines.

Experimental Section

General: NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^1H and ^{13}C acquisition, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^1H NMR; $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionization techniques. Analytical TLC was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation, $KMnO_4$, or vanillin stains. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The enantiomeric excess (*ee*) of the products was determined by chiral stationary-phase HPLC (Daicel Chiralpak AS/AD and Daicel Chiralcel OD/OJ columns). Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC) silica gel (silica gel 60, 230–400 mesh, Fluka) was used.

General procedure for synthesis of chiral 2,3,3,5-tetrasubstituted 2,3-dihydro-1*H*-pyrroles: A solution of catalyst **3c** (1 mol%, 60 μL, 9 mg mL^{-1} in $CHCl_3$) was added to a solution of **2** (0.1 mmol) and imine **1** (0.15 mmol) in $CHCl_3$ (2 mL) at −60°C. The reaction was stirred at −60°C for 22 h. The mixture was allowed to warm to RT and *p*-toluensulfonic acid monohydrate (10 mol%) and PPh_3AuNTf_2–1/2toluene (5 mol%) were added sequentially. The reaction was stirred at RT until full conversion (3–5 h) to product **5** (TLC, CH_2Cl_2/pentane, 2:1). Filtration through a short pad of silica (CH_2Cl_2) followed by FC on silica gel afforded the enantioenriched product **5**.

General procedure for synthesis of optically active 2,3,3,5-tetrasubstituted 1-pyrrolines: Compound **5** was dissolved in a CH_2Cl_2/TFA (5:1) (0.03 M) mixture and stirred for 1 h at room temperature. The solvent was evaporated, and TFA removed as an azeotrope with toluene (2×1 mL). The residue was dissolved in EtOAc (0.5 mL), extracted with a sat. Na_2CO_3 solution, water, dried over Na_2SO_4, and evaporated to yield the pure product **6**.

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