Asymmetric Synthesis

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Asymmetric Synthesis of Spiropyrazolones by Sequential Organo- and Silver Catalysis

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Dedicated to Professor Steven Victor Ley on the occasion of his 70th birthday

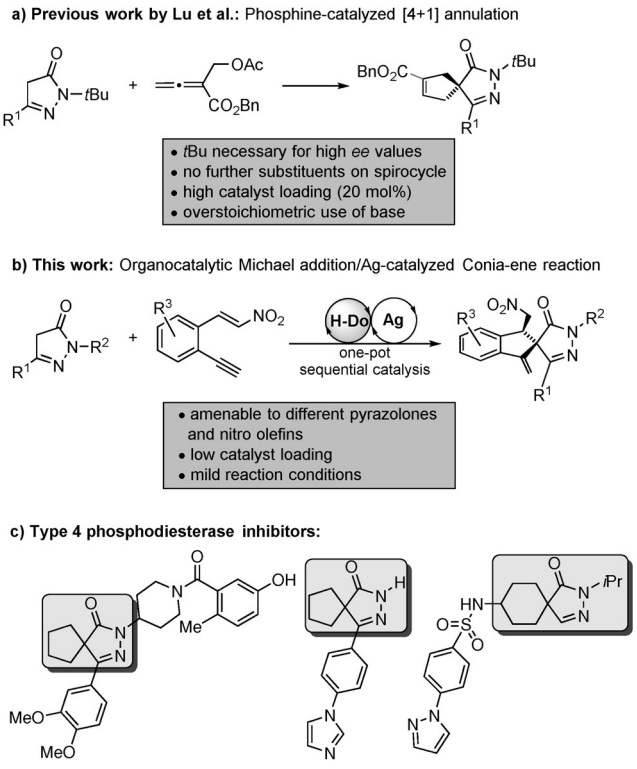
Abstract: *A stereoselective one-pot synthesis of spiropyrazolones through an organocatalytic asymmetric Michael addition and a formal Conia-ene reaction has been developed. Depending on the nitroalkene, the 5-exo-dig-cyclization could be achieved by silver-catalyzed alkyne activation or by oxidation of the intermediate enolate. The mechanistic pathways have been investigated using computational chemistry and mechanistic experiments.*

From its basic inception in the late seventies, the Conia-ene reaction has turned into a viable synthetic tool for organic chemists by enabling the facile formation of five- or six-membered carbo- and heterocycles.[1] More recently, asymmetric procedures have emerged which further exemplify the synthetic utility of this well-known pericyclic reaction. Basically, all of these procedures rely on similar strategies, either applying a cooperative heterobimetallic system with a chiral ligand in the coordination sphere of the harder metal[2] or by using a metal which enables the concurrent activation of the alkyne and the enol moiety together with a chiral ligand.[3]

Our group has become interested by the combination of transition-metal and organocatalysis for the asymmetric synthesis of annulated heterocycles.[4] Although we originally focused our investigations on gold catalysis,[5] we have been recently intrigued by silver catalysis and its largely untapped potential in sequential and relay catalysis.[6–8] Ag^I salts represent an inexpensive alternative to other carbophilic transition metals commonly used for the electrophilic activation of alkynes such as gold or platinum.[9] Moreover, unlike cationic gold(I) complexes, silver salts can be easily combined with organocatalysts including primary amines and squaramides, without mutual catalyst deactivation or deteriorating reaction rates.[10] As a consequence, there is no need for further additives or harsher reaction conditions in order to retrieve the active species of the metal catalyst.

Following this approach, we reported on the asymmetric synthesis of pyrano-annulated pyrazoles originating from alkyne-tethered nitroolefins and pyrazolones.[6b] Given the ambident nucleophilicity of pyrazolones, we wondered if the formation of 4-spiropyrazolones was possible through the subsequent addition of the enol hydrazide to the metal-activated alkyne after the initiating Michael addition of the pyrazolone to the nitroolefin. We envisioned that such an addition would be feasible by increasing the distance between the Michael acceptor moiety and the alkyne (Scheme 1b).

Indeed, the planned strategy turned out to be a convenient one-pot procedure for the complementary synthesis of five-membered 4-spiropyrazolones, which have been recently



Scheme 1. General outline of the strategy employed herein and previous related work (H-Do denotes hydrogen-bonding donor).

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distinguished as efficient phosphordiesterase inhibitors (Scheme 1 c).[11] Interestingly, most literature-known organocatalytic syntheses are limited to the generation of six-membered spiro derivatives.[12,13] There is only one precedence by Lu and co-workers who employed a phosphine-catalyzed [4+1] annulation using pyrazolones and allenoates (Scheme 1 a).[14] However, this procedure suffers from high catalyst loadings and it is limited to pyrazolones with bulky substituents (R^1 = aromatic; R^2 = *t*Bu). Moreover, the reaction has only been probed for a single allenoate, and it is unclear whether further substituents on the spirocycle could potentially be introduced.

Our optimization studies showed that the best results were achieved by reacting pyrazolone and nitroalkene in chloroform at −40 °C in the presence of 1 mol % of a dihydroquinine-derived squaramide DHQN-SA1 and 3 mol % of Ag_2O (see the Supporting Information for optimization tables; see Scheme 2 for the structure of DHQN-SA1). The efficiency of the reaction appeared to be also influenced by the solubility of substrates and the intermediates, as well the stability of the Michael adduct in solution.

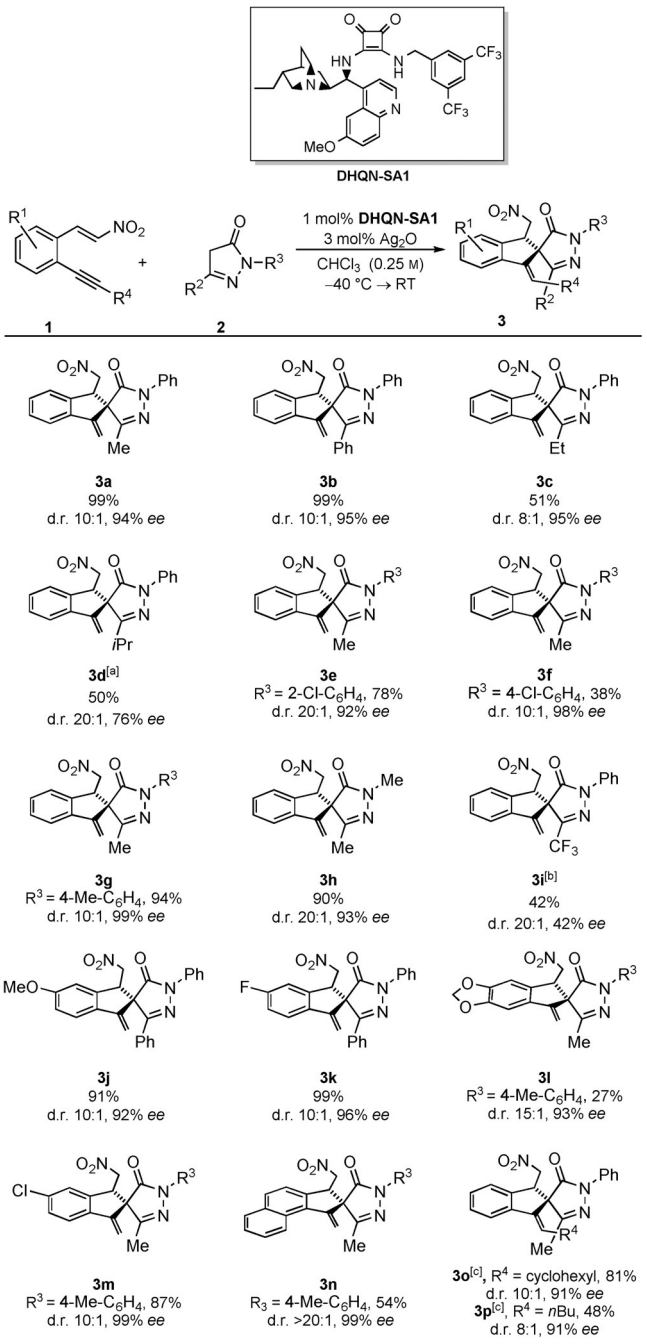
With the optimized reaction conditions in hand, different substrates were probed to demonstrate the general applicability of the sequential reaction (Scheme 2).[15]

In general, excellent yields and enantioselectivities along with good to excellent diastereoselectivities were obtained for differently substituted pyrazolones (Scheme 2; **3a**, **3b**, **3e**–**h**). Some pyrazolones as well as the corresponding Michael adducts showed a limited solubility in $CHCl_3$, so that either different solvents had to be applied or the reaction had to be conducted at higher temperatures. Thus, lower yields and selectivities were detected for these examples. The developed procedure was also amenable to differently substituted nitroalkenes with terminal alkynes resulting in the formation of spiropyrazolones in high yields and excellent stereoselectivities. In general, the electronic nature of the substituent did not influence the outcome of the reaction, however, bulky nitroolefins led to lower yielding reactions (Scheme 2; products **3l** and **3n**). The application of nitroalkenes with internal alkynes bearing aliphatic substituents was also feasible, although higher catalyst loadings had to be used to achieve comparable results (**3o**, **3p**).

Interestingly, we found that the cyclization for the intermediate Michael adducts originating from nitroolefins which contain internal alkynes with an additional phenyl substituent occurred without the presence of metal salts as catalysts (Table 1). Thus, it was feasible to obtain the corresponding spiropyrazolones in good to excellent yields and stereoselectivities. It should be noted though that these reactions were conducted at room temperature because the Michael addition was not feasible at lower temperatures.

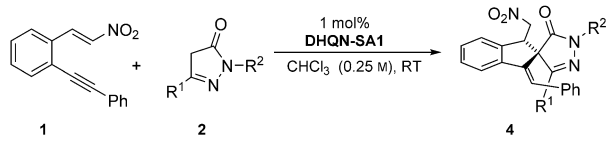
The absolute configuration of the obtained spiropyrazolones **3** and **4** as well as the formation of the *Z* diastereomer were confirmed by X-ray diffraction analysis of suitable crystals from derivatives **3h** and **4a** (Figure 1; see also the Supporting Information).[19]

To gain insight into the mechanism and origin of the selectivity, we turned to computational studies. Following the initial Michael addition step, the generated intermediate **5a** could potentially be neutral or reside as an anionic species (enol or enolate, respectively; see Figure 2). We considered both possibilities and studied the pathways for ring closure in an *exo* and *endo* fashion, applying the CPCM (DCM) M06/def2-TZVP//B3LYP/6-31G(d) level of theory.[16,17] Our data suggest that the neutral, uncatalyzed pathway has a prohibitively high barrier ($\Delta G^{\ddagger} = 29.3$ kcal mol^{-1}, relative to **5a^H**) to take place under the applied reaction conditions.[18]



Scheme 2. Substrate scope for the sequential catalysis. [a] The reaction was performed in toluene at room temperature. [b] The reaction was performed at room temperature. [c] In the presence of 10 mol % Ag_2O. General reaction conditions: **1** (0.33 mmol), **2** (0.3 mmol), DHQN-SA1 (1 mol %), Ag_2O (3 mol %), $CHCl_3$ (1.2 mL), −40 °C to RT.

Table 1: Substrate scope for the nitroalkene bearing an internal alkynes with a phenyl substituent.[a]



4	R^1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
a	Me	Ph	99	10:1	90
b	Et	Ph	83	>20:1	93
c	*i*Pr	Ph	74	>20:1	92
d	Ph	Ph	95	6:1	91
e	Me	2-Cl-C_6H_4	73	10:1	82
f	Me	4-Me-C_6H_4	89	10:1	99
g[e]	Me	Me	59	20:3	86

[a] Reaction conditions: **1** (0.33 mmol), **2** (0.3 mmol), DHQN-SA1 (3 mol%), $CHCl_3$ (1.2 mL), RT, 1–2 h. [b] Yield of **4** after flash chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC using a chiral stationary phase. [e] The formation of small amounts of an additional diastereomer or regioisomer was detected.

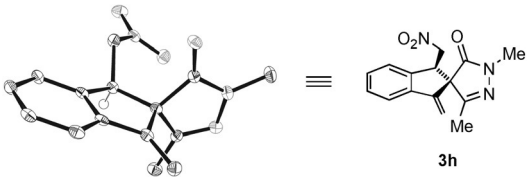


Figure 1. X-ray crystal structure of (*R*,*R*)-**3h**.[19]

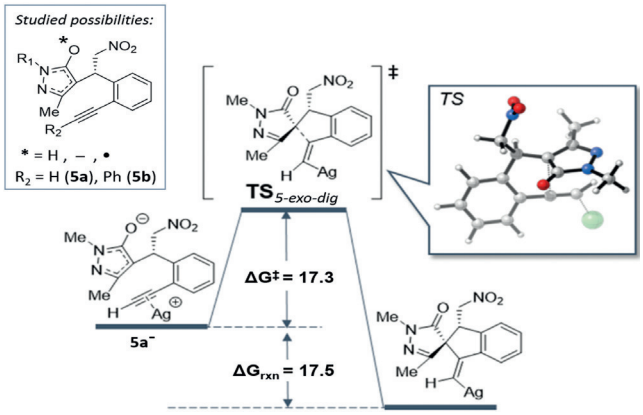


Figure 2. Calculated reaction pathway for the deprotonated intermediate under silver(I) catalysis. Calculated at the CPCM (DCM) M06/def2-TZVP// B3LYP/6-31G(d) (LANL2DZ for Ag) level of theory. Free energies in kcal mol^{-1}.

The anionic pathway is characterized by a lower activation free energy barrier ($\Delta G^{\ddagger} = 21.7$ kcal mol^{-1}), favoring the 5-*exo-dig* cyclization by $\Delta\Delta G^{\ddagger} = 4.9$ kcal mol^{-1}. However, the process suffers from being highly endergonic ($\Delta G_{rxn} = 20.5$ kcal mol^{-1}) and thermodynamically strongly disfavored.(see the Supporting Information for more details). In contrast, in the presence of Ag^+,[20] the same 5-*exo-dig* cyclization is calculated to become thermodynamically strongly favored ($\Delta G_{rxn} = -17.5$ kcal mol^{-1}), and exhibits a significantly lower activation barrier ($\Delta G_{rxn} = 17.3$ kcal mol^{-1}; see Figure 2).[21]

A special case is the phenyl-substituted substrate **1** (R^1 = H, R^4 = Ph), that we experimentally found to react even under silver-free conditions, albeit more slowly. This silver-free process was found to occur only in the presence of oxygen, strongly suggesting that a radical pathway upon oxidation may also be possible. In accordance with this, we calculated a relatively facile and slightly exergonic cyclization of the radical derived from the Michael addition intermediate (**5b**$^{\bullet}$; $\Delta G^{\ddagger} = 11.1$ kcal mol^{-1}) at the CPCM (DCM) M06/def2-TZVP//ROB3LYP/6-31G(d) level of theory. On the other hand, for the unsubstituted substrate **1** (R^1 = H, R^4 = H), which did not yield any product under Ag-free aerobic conditions, the analogous process is predicted to be significantly less favored, both kinetically ($\Delta G^{\ddagger} = 20.0$ kcal mol^{-1}) and thermodynamically ($\Delta G_{rxn} = +9.0$ kcal mol^{-1}), likely therefore favoring a nonproductive side reaction under these conditions (see the Supporting Information for details).

Consequently, the sequential procedure can be described as a combination of a squaramide-catalyzed Michael addition and a silver-catalyzed Conia-ene reaction. Similar to our previous work,[6b] the organocatalyzed asymmetric reaction may proceed through the formation of a ternary complex in which the nitroalkene undergoes electrophilic activation by hydrogen-bond formation to the squaramide scaffold (Figure 3).[22,23]

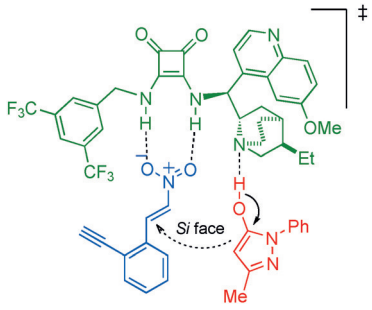


Figure 3. Proposed transition state for the organocatalytic Michael addition.

In summary, we have developed a one-pot procedure for the asymmetric synthesis of five-membered spiropyrazolones starting from readily available pyrazolones and alkyne-tethered nitroalkenes. The syntheses of the desired products proceed in high yields and stereoselectivities under mild reaction conditions at comparatively low catalyst loadings. Considering that different substituents on the nitroolefin and pyrazolone substrates are tolerated, this method circumvents the formerly known limitations of similar spiropyrazolone syntheses.

Experimental Section

A suspension of nitroolefin **1a** (57 mg, 0.33 mmol, 1.1 equiv), pyrazolone **2a** (52 mg, 0.3 mmol, 1.0 equiv), DHQN-SA1 (1 mol%), and Ag_2O (3 mol%) in $CHCl_3$ (1.2 mL) was stirred at −40 °C until

complete conversion of the substrates was achieved as indicated by TLC monitoring. The mixture was allowed to warm to room temperature and was stirred for an additional two hours. The spiropyrazolone **3a** was obtained after flash chromatography on silica (eluent: *n*-pentane/Et_2O) as a colorless solid (104 mg, 99%).

Acknowledgements

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Keywords: asymmetric synthesis · Conia-ene reaction · organocatalysis · pyrazolones · silver catalysis

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[18] Moreover, the neutral, uncatalyzed pathway would yield the product in the opposite alkene stereochemistry from that experimentally detected.

[19] CCDC 1420480 (**3h**) and 1420481 (**4a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[20] We used Ag^+ in the calculations, as experiments showed that $AgBF_4$ was similarly effective in catalyzing the reaction as Ag_2O.

[21] There are two potential scenarios for the Ag^+ catalyzed pathway, namely neutral and cationic. In both cases, calculations indicate that the activation barrier of the cyclization step is significantly lowered. However, computations suggest that the cationic pathway is strongly endergonic and that the formation of the *endo* product would be preferred, which is in contrast to experiments. Therefore, it is likely that the preferred pathway is the neutral one (see Figures S4 and S5).

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