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Letter

Mn- and Co-Catalyzed Aminocyclizations of Unsaturated Hydrazones Providing a Broad Range of Functionalized Pyrazolines

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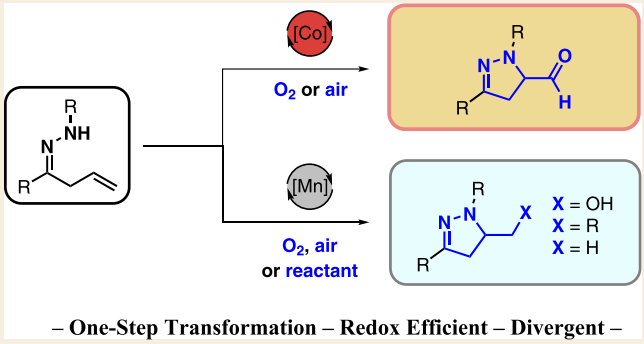
ABSTRACT: Manganese- and cobalt-catalyzed aminocyclization reactions of unsaturated hydrazones are reported. Whereas manganese catalysis provides access to pyrazoline and tetrahydropyridazine alcohols, cobalt catalysis for the first time paves the way for the selective formation of pyrazoline aldehydes. Furthermore, various functional groups including hydroperoxide, thiol derivatives, iodide, and bicyclopentane may be introduced via manganese-catalyzed ring-forming aminofunctionalization. A progesterone receptor antagonist was prepared using the aminocyclization protocol.

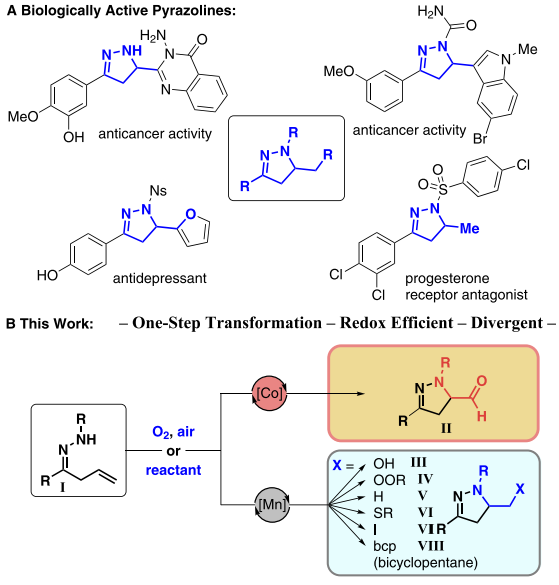


KEYWORDS: *Aminocyclization, Cobalt, Manganese, Pyrazolines, Hydrazones, Oxygen, Aldehyde*

Azoles such as pyrazoles are important building blocks in modern pharmaceutical and agrochemical industry.[1−6] Partially saturated counterparts, in particular 2-pyrazolines, are gaining recognition as promising scaffolds,[7,8] as they offer great opportunity for structural diversification, which has proven to be key in modern drug development.[9,10] In parallel, there has been great interest in building blocks that provide possibilities for design beyond the two-dimensional space of traditional (hetero)aromatic rings.[9,10] Accordingly, leads incorporating 2-pyrazolines have appeared in drug discovery programs for treatment of a wide range of diseases, including cancer,[8b,d] diabetes,[8g] and malaria.[8e] They have also shown anti-inflammatory,[8c] -microbial,[8e] and -fungal activity (Scheme 1A).[8f] Hence, approaches that lead to this scaffold with diverse functional groups are especially valuable. Herein we report selective manganese- and cobalt-catalyzed aminocyclization reactions of unsaturated hydrazones **I** that provide a wide variety of functionalized pyrazolines, including aldehydes, alcohols, peroxide, thiol derivatives, iodide, and bicyclopentane (**II**−**VIII**, Scheme 1B).

Pyrazolines have commonly been prepared via 1,3-dipolar cycloadditions[11,12] or condensation reactions of enones and hydrazines.[11b,13,14] Recently, Cu-catalyzed oxidative cyclization of unsaturated hydrazones has been reported to give pyrazolines.[15] However, this process affords a mixture of aldehydes **II** (20%), alcohols **III** (18%), and hydroperoxides **IV** (40%), thus requiring a subsequent reductive step to convert the mixture into alcohol products. There have also been reports on the use of acridinium[16] and ruthenium[17] photocatalysis to furnish pyrazolines, such as **III** and **V**.[18−20] Collectively, these approaches demonstrate the general interest

Scheme 1. Biologically Active Pyrazolines and Cyclization Reactions of Unsaturated Hydrazones



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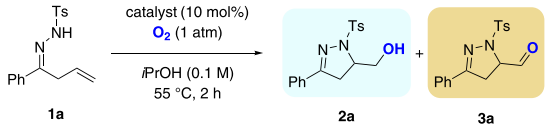
in methods for the preparation of functionalized pyrazolines. However, convenient access is desirable not only to alcohols but also to an expanded set of products that include other groups. These would be especially useful because they may serve as linchpins for further synthetic elaboration. In this respect, selective and efficient access to aldehydes, such as **II** in Scheme 1B, has not been reported, despite the fact that they act as a gateway to other functionalities, such as carboxylic acids, amides, nitriles, amines, and heterocycles. Chemler reported the aerobic copper-catalyzed cyclization of 4-pentenylsulfonamides to yield 2-formylpyrrolidines, which were then subjected to oxidative C−C bond cleavage and further transformed into 2-pyrrolidinones.[21,22]

Catalysis by first-row transition metals has gained significant attention because of their low cost and natural abundance.[23] The use of manganese and cobalt catalysis remains relatively underexplored for olefin functionalizations in comparison with other transition metals such as copper, palladium, and nickel,[24−26] yet it offers great opportunities. We have been inspired by one of the earliest examples of preparatively useful cobalt-catalyzed olefin functionalization, namely, the Mukaiyama hydration,[27,28] and related processes.[29,30]

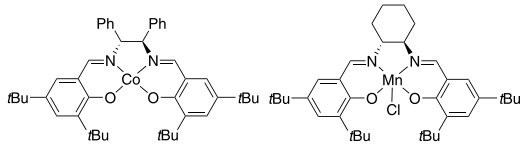
Our prospecting studies commenced by examination of hydrazone **1a** as a prototype in a variety of cyclization reactions (Table 1). Extensive optimization studies[31] revealed that

Table 1. Selected Optimization Results for the Mn- and Co-Catalyzed Cyclizations



1a 2a 3a

entry	catalyst	yield **2a**[a]	yield **3a**[a]
1	$Mn(acac)_3$	31%	15%
2	$Mn(dpm)_3$	**79%** (78%)[b]	1.6%
3	$Mn(dpm)_3$[c]	68%	3.1%
4	$Mn(dpm)_3$[d]	65%	6%
5	Mn(salen) **5**[e]	-	-
6	Co(salen) **4**[e]	24%[b]	**70%**[b]



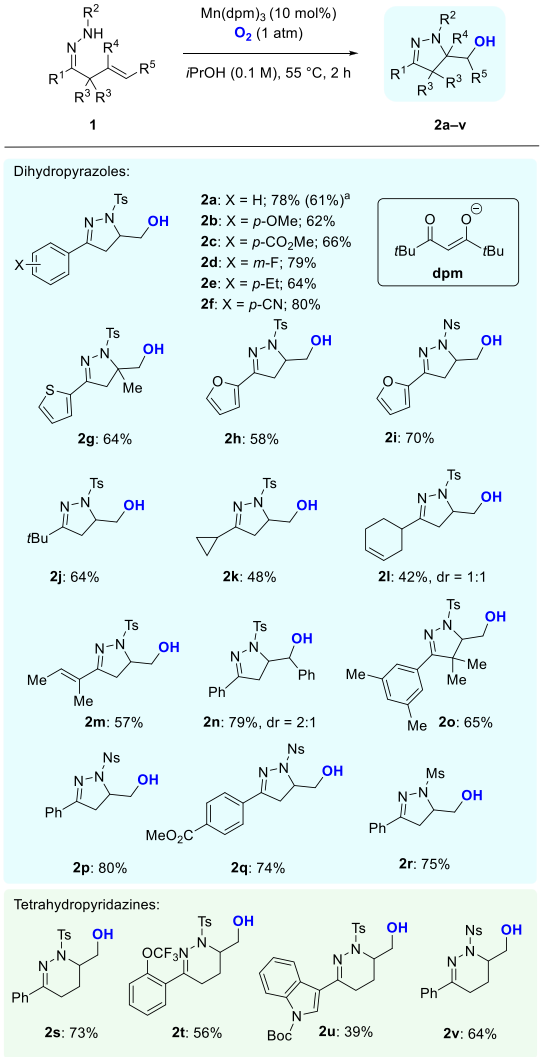
4 5

[a]Determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard. [b]Isolated yield. [c]Air was continuously introduced into the reaction mixture. [d]The reaction was conducted at 25 °C for 12 h. [e]The reaction was conducted at 25 °C for 1 h.

treatment of **1a** with $Mn(acac)_3$ (10 mol %) under an oxygen atmosphere (1 atm) in isopropanol (0.1 M) at 55 °C for 2 h afforded pyrazoline alcohol **2a** in 31% yield alongside the corresponding aldehyde **3a** in 15% yield (Table 1, entry 1).[32] Switching to $Mn(dpm)_3$ (dpm = dipivaloylmethanato) significantly improved the reaction outcome and selectivity, providing **2a** in 79% yield and **3a** in merely 1.6% yield (**2a**:**3a** ratio = 98:2) (entry 2). The use of air via a gas inlet instead of a pure oxygen atmosphere furnished alcohol **2a** in 68% yield (entry 3). This result was satisfying, as especially on larger scales the handling of molecular oxygen can be hazardous.[33] Lowering the reaction temperature to 25 °C was also feasible with an elongated reaction time (12 h, 65% yield; entry 4). In examining other catalysts (see the Supporting Information), we observed that cobalt salen **4** resulted in a change in the reaction outcome, affording aldehyde **3a** in 70% yield, whereas manganese salen **5** did not lead to product formation (entries 5 and 6).[31,34]

With the optimized reaction parameters in hand for cyclization and selective formation of alcohols, the scope of the reaction was investigated (Scheme 2). Various β,γ-

Scheme 2. Mn-Catalyzed Cyclizations



[a]The reaction was conducted on a 4 mmol scale.

unsaturated aryl- and heteroarylhydrazones were submitted to the established reaction conditions, and N-heterocycles **2a**−**i** were obtained in 58−80% yield. Esters and nitriles were well-tolerated in the cyclization reaction, and no difference in reactivity was observed for substrates incorporating electron-donating and -withdrawing substituents. The use of alkylhydrazones as substrates led to the formation of pyrazolines **2j**−**l** in 42−64% yield. In the presence of additional olefins, which could participate in competitive cyclizations, only 5-exo-trig

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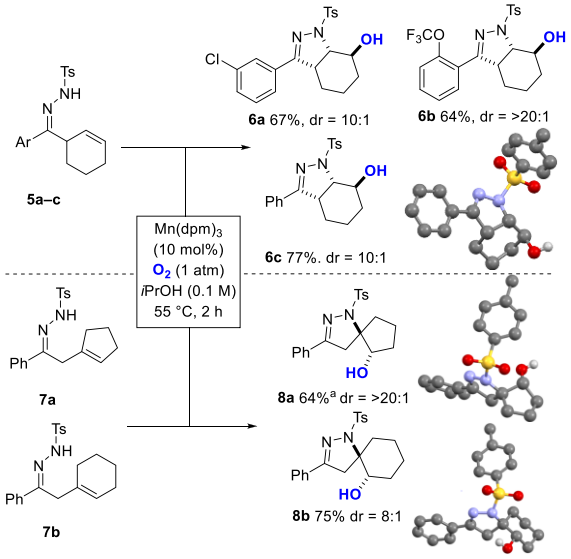
cyclization was observed, and N-heterocycles **2l** and **2m** were isolated in 42% and 57% yield, respectively. Substrates with substituents on the alkyl chain (**1g**, **1n**, and **1o**) were also employed and provided, after cyclization, pyrazolines **2g**, **2n**, and **2o** in 64−79% yield. Replacing the *N*-tosyl group with *N*-nosyl (*p*-nitrophenylsulfonyl) or *N*-mesyl (methylsulfonyl) was also possible, giving rise to pyrazolines **2i** and **2p**−**r** in 70−80% yield. When *γ*,*δ*-unsaturated hydrazones were submitted to the reaction conditions, tetrahydropyridazines **2s**−**v** were obtained in 39−73% yield.

We then investigated substrates in which the alkene partner was embedded within a ring, which would lead to ring-fused or spiro-pyrazolines (Scheme 3). Hydrazones **5a**−**c** as starting

Scheme 3. Preparation of Fused and Spiro Pyrazolines

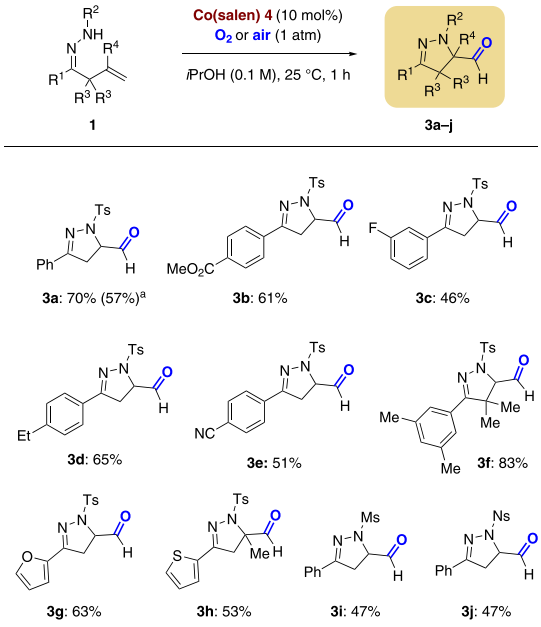


[a]$Mn(dpm)_3$ (20 mol %) was used.

materials provided valuable 5,6-fused bicyclic rings **6a**−**c** possessing an anti relative configuration (64−77% yield, dr 10:1 to >20:1), as determined by ^{1}H NMR, X-ray, and 1D NOE data (Scheme 3).[35,36] When cyclopentene- and cyclohexene-substituted hydrazones **7a** and **7b** were used, [4.4] and [4.5] spirocycles **8a** and **8b** were prepared in high yields with excellent diastereoselectivity (64% and 75% yield, dr >20:1 and 8:1, respectively; Scheme 3).

During the optimization studies aimed at preparation of the primary alcohol product shown in Table 1, we observed that the formation of aldehyde **3a** was preferred with the use of Co-salen **4** as catalyst (see Table 1, entry 6). Given the rather limited number of examples of cyclization reactions of olefins that produce aldehydes, we set out to investigate the scope of this transformation (Scheme 4). Various functional groups including nitriles and esters were well-tolerated, yielding aldehydes **3a**−**f** in 46−83% yield.[37] Replacing the oxygen atmosphere by air via a gas inlet led to **3a** in 57% yield. When furan and thiophene hydrazones were employed, pyrazolines **3g** and **3h** were isolated in 63% and 53% yield, respectively. Other sulfonamides could be used, such as *N*-mesyl and *N*-nosyl, yielding aldehydes **3i** and **3j**, both in 47% yield (Scheme 4). We speculate that the cobalt catalyst mediates cyclization, formation of a terminal hydroperoxide, and its collapse to aldehydes **3a**−**j**.[38]

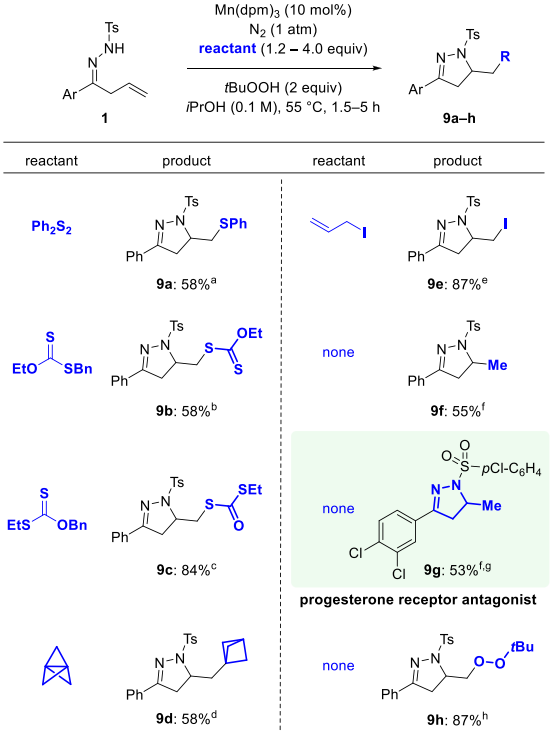
Scheme 4. Co-Catalyzed Cyclizations



[a]Air was continuously introduced into the reaction mixture.

We then proceeded to examine the use of other reactive traps instead of oxygen (Scheme 5). After prospecting experiments, we found a standard set of conditions in which stirring **1a** with various reactants in the presence of $Mn(dpm)_3$

Scheme 5. Mn-Catalyzed Aminofunctionalizations



[a]Diphenyl disulfide as the reactant. [b]*S*-benzyl *O*-ethyl carbonodithioate as the reactant. [c]*O*-benzyl *S*-ethyl carbonodithioate as the reactant. [d][1.1.1]propellane as the reactant. [e]allyl iodide as the reactant. [f]No reactant. [g]$Mn(dpm)_3$ (30 mol %) was used. [h]No reactant; DCE was used as the solvent.

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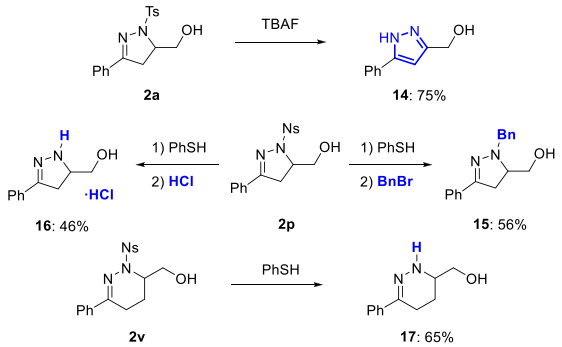
(10 mol %) and *t*BuOOH (2 equiv) in *i*PrOH under N_2 (1 atm) gave a variety of adducts. In the presence of diphenyl disulfide (2 equiv) thioether **9a** was formed in 58% yield. The reaction of **1** with *S*-benzyl *O*-ethyl carbonodithioate and *O*-benzyl *S*-ethyl carbonodithioate afforded xanthate **9b** and carbonodithioate **9c** in 58% and 84% yield, respectively. With [1.1.1]propellane, bicyclopentane derivative **9d** was obtained in 58% yield. The use of allyl iodide afforded primary iodide **9e** in 87% yield. Interestingly, in the absence of additional reactants, treatment of **1a** with $Mn(dpm)_3$ (10 mol %) and *t*BuOOH (2 equiv) in *i*PrOH under N_2 (1 atm) provided **9f** in 55% yield.[39] When the appropriate unsaturated hydrazone was employed as the starting material it was possible to prepare pyrazoline **9g**, a progesterone receptor antagonist,[8a] in 53% yield. In cyclizations leading to **9f** and **9g**, *i*PrOH acts as a hydrogen donor, as described in the early work of Mukaiyama.[34,40] When the reaction was conducted in DCE instead of *i*PrOH, *tert*-butylhydroperoxide quenched the reactive intermediate to give dialkyl peroxide **9h** in 87% yield (Scheme 5).

Finally, various synthetic transformations were performed using pyrazoline and tetrahydropyridazine alcohols (Scheme 6).[35] Reaction of **2a** with Bu_4NF led to elimination of the *N*-tosyl group, which provided pyrazole **14** in 75% yield. When *N*-nosyl pyrazoline **2p** was treated with thiophenol at room temperature in the presence of K_2CO_3 followed by benzyl bromide, pyrazoline **15** was obtained in 56% yield.[41] It was also possible to prepare the corresponding hydrochloride salt **16** in 46% yield by addition of 2 M HCl in dioxane after sulfonamide cleavage.[42] Removal of the *N*-nosyl group from tetrahydropyridazine **2v** could also be carried out, affording azine **17** in 65% yield (Scheme 6).

Scheme 6. Derivatization of the Pyrazolines and Tetrahydropyridazine



In summary, we have disclosed manganese- and cobalt-catalyzed cyclization reactions of unsaturated hydrazones that gave divergent access to a range of complex and highly functionalized N-heterocycles. Whereas aerobic manganese catalysis led to the formation of pyrazoline and tetrahydropyridazine alcohols, a cobalt–salen catalyst for the first time allowed the preparation of pyrazoline aldehydes. Addition of various reactants to the cyclization reaction paved the way for the formation of a variety of functionalized pyrazolines as well as a progesterone receptor antagonist. Finally, synthetic transformations of the prepared products were performed, demonstrating the utility of the cyclization protocol. We are in the process of further developing cyclization reactions that lead to versatile aldehyde products, and the results will be reported as they become available.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.1c00176.

- Full experimental details, crystallographic data, and ^1H and ^{13}C spectra (PDF)
- Crystallographic data for **8a** (CIF)
- Crystallographic data for **6c** (CIF)
- Crystallographic data for **8b** (CIF)
- Crystallographic data for **9d** (CIF)
- Crystallographic data for **14** (CIF)

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Notes

The authors declare no competing financial interest.

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(36) CCDC 2078368 (**6c**), CCDC 2078369 (**8a**), CCDC 2078370 (**8b**), CCDC 2078371 (**9d**), and CCDC 2078372 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(37) Reduction of **3a** to alcohol **2a** using $NaBH_4$ (1.1 equiv, THF (0.1 M), 25 °C, 1 h) followed by chiral SFC analysis of the alcohol did not show enantiomeric enrichment.
(38) When the cobalt-catalyzed reaction was conducted at 0 °C, exclusive formation of the hydroperoxide was first observed. Upon warming to room temperature, formation of aldehyde **3a** and alcohol **2a** took place. The hydroperoxide was not observed when $Mn(dpm)_3$ was used. We postulate that while in both reactions the hydroperoxide may be formed, in the presence of Mn it undergoes rapid reduction to the alcohol, thus precluding oxidation to the aldehyde.
(39) We were also interested to find out whether **9f** can be prepared via a condensation reaction. However, treatment of (*E*)-1-phenylbut-2-en-1-one with *N*-tosylhydrazide (1.1 equiv) in MeOH at 25 °C for 12 h gave **9f** in merely 5% yield.
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(42) Also, HCl salt **16** is thermally sensitive and does not store well.

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