

Dichotomy of Reductive Addition of Amines to Cyclopropyl Ketones vs Pyrrolidine Synthesis

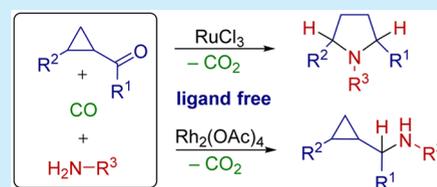
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S Supporting Information

ABSTRACT: An interesting catalytic dichotomy was discovered: switching between simple ligand-free catalysts leads to fundamentally different outcomes of reductive reaction between amines and α -carbonylcyclopropanes. Whereas a rhodium catalyst leads to the traditional reductive amination product, ruthenium catalysis enables a novel reaction of pyrrolidine synthesis via ring expansion. The protocols do not require an external hydrogen source and employ carbon monoxide as a deoxygenative agent. The developed methodologies are perfectly compatible with a number of synthetically important functionalities such as ester, carboxyl, bromo, and Cbz moieties.



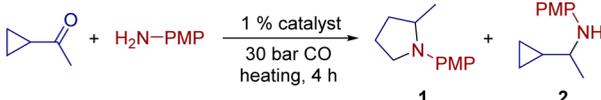
The past decade can be called the golden age of donor–acceptor (D–A) cyclopropane chemistry.¹ Despite the fact that D–A cyclopropanes have been known since the 1980s,² the unique synthetic potential of these compounds has become fully appreciated only during recent years.³ D–A cyclopropanes can undergo various notable transformations, such as [2 + 2], [3 + 2], [3 + 3], [4 + 2], and [4 + 3] cycloadditions, annulations, and ring openings that lead to pyrroles, furans, amines, silylenolates, lactones, etc. The natural limitation of some of D–A cyclopropane chemistry is that both an electron-donating and an electron-withdrawing group have to be present in the cyclopropyl ring in order to provide a synergistic activation effect. In contrast, we have been excited about opportunities to expand the types of transformations which usually require a special substitution pattern of the cyclopropyl ring onto less specialized cyclopropane substrates.⁴

Recently, we have demonstrated the unique potential of carbon monoxide as a reducing agent on the examples of efficient atom-economical transformations, such as reductive amination of aldehydes^{5a,c,6} and ketones^{5d} as well as reductive Knoevenagel condensation.^{5b} The developed methodologies are notable for favorable environmental profiles, synthetically useful functional group compatibility, and access to sterically challenged molecules; synthetic superiority over conventional highly selective reagents (e.g., sodium cyanoborohydride) was vividly demonstrated.⁶ The net effect of the reported protocols corresponds to reductive formation of a single C–C or C–N bond, which represents highly useful yet synthetically simple transformations. On the contrary, herein we report a novel methodology which likewise takes advantage of the reductive potential of carbon monoxide⁶ but at the same time represents conceptually more advanced chemistry compared to the previously described contributions to the field.^{5–9}

In a Rh-catalyzed reaction between methyl cyclopropyl ketone and *p*-anisidine, we were excited to find that, in addition

to the expected reductive amination adduct **2** (36%), comparable amounts of pyrrolidine **1** were also formed (20%). This feature could provide the grounds for the development of an interesting and synthetically valuable methodology of pyrrolidine synthesis, and therefore, we initiated efforts to shift the ratio of the products in the model reaction toward the desired product **1**. Solvent screening (Table 1, entries 1–8) demonstrated that highest pyrrolidine content could be achieved in tetrahydrofuran, diethyl ether, and 2-propanol (Table 1, entries 1, 6, and 8), yet the product yields remained low. We hypothesized that pyrrolidine formation could be the result of the rearrangement of initially formed traditional adduct **2** and tested if elevated temperature could favor product **1**. Surprisingly, increasing the temperature resulted in higher yields of cyclopropane **2** (Table 1, entries 1, 9–12); bringing the temperature from 110 to 130 °C changed the pyrrolidine–cyclopropane ratio from 1:1.8 to 1:4.4. On the contrary, when we decreased the temperature to 100 °C, pyrrolidine **1** became the main product with 6-fold higher yield over the cyclopropane. No pyrrolidine was detected when pure **2** was subjected to the reaction conditions in dioxane, THF, or water, which indicated that the two products were formed via independent pathways. While keeping the reaction temperature at 130 °C in line with the observed trend, we found dioxane to be the best media for selective preparation of the traditional product: 92% yield of compound **2** could be detected, which was accompanied by only trace amounts of the pyrrolidine counterpart (Table 1, entry 13). At this point, however, it became obvious that the Rh-based catalytic system had no potential for optimization into a preparative tool for pyrrolidine synthesis from cyclopropyl ketones.

Received: September 29, 2016

Table 1. Catalyst and Solvent Optimization for the Preparation of Pyrrolidines vs Cyclopropylamines


entry ^a	catalyst	temp (°C)	solvent	1 (%)	2 (%)
1	Rh ₂ (OAc) ₄	110	THF	20	36
2	Rh ₂ (OAc) ₄	110	solvent free	2	0
3 ^d	Rh ₂ (OAc) ₄	110	MeCN	3	0
4	Rh ₂ (OAc) ₄	110	MeOH	3	0
5	Rh ₂ (OAc) ₄	110	water	12	8
6	Rh ₂ (OAc) ₄	110	Et ₂ O	28	56
7	Rh ₂ (OAc) ₄	110	dioxane	0	65
8	Rh ₂ (OAc) ₄	110	ⁱ PrOH	16	44
9	Rh ₂ (OAc) ₄	100	THF	24	4
10	Rh ₂ (OAc) ₄	120	THF	16	72
11	Rh ₂ (OAc) ₄	130	THF	18	80
12	Rh ₂ (OAc) ₄	140	THF	18	80
13	Rh ₂ (OAc) ₄	130	dioxane	trace	92
14 ^b	RuCl ₃	160	THF ^c	89	6
15 ^b	RuCl ₃	160	solvent free	75	18
16 ^b	RuCl ₃	160	MeCN	40	4
17 ^b	RuCl ₃	160	MeOH	80	10
18 ^b	RuCl ₃	160	Et ₂ O	76	21
19 ^b	RuCl ₃	160	toluene	72	25
20 ^b	RuCl ₃	160	dioxane	59	15
21 ^b	RuCl ₃	160	^t BuOH	48	16
22 ^b	RuCl ₃	160	EtOH	76	16
23 ^b	RuCl ₃	160	water	92	8
24 ^d	RuCl ₃	160	water	91	trace

^a100 mol % of methyl cyclopropyl ketone, 100 mol % of *p*-anisidine, 1 mol % of Rh₂(OAc)₄, 4 h, or 1 mol % of RuCl₃, 5 h. Yields were determined by ¹H NMR with internal standard. ^b4 mol % of RuCl₃ were used over 5 h. ^cObtained with a particularly rigorous exclusion of water. ^d24 h.

We switched our attention to identification of an alternative catalyst which would favor formation of product 1. After screening a number of metal complexes (such as PtO₂, Pd(PPh₃)₄, Pd(OAc)₂, Re₂(CO)₁₀, Ir₄(CO)₁₂, [(COD)IrCl]₂, CpIrI₂, RhCl₃, Rh₆(CO)₁₆, RuCl₃, see the [Supporting Information](#)), we were delighted to find ruthenium trichloride as a basis for an orthogonal catalytic system. In contrast to rhodium acetate, ruthenium-mediated reaction demonstrated an inverted selectivity profile (Table 1, entry 14).

Solvent screening (Table 1, entries 14–23) showed that among organic solvents the best results could be achieved in THF with very rigorous exclusion of water (Table 1, entry 14). However, an even higher yield of 1 was obtained in pure water (entry 23). The effect of the water content on the reaction outcome is therefore very peculiar: both anhydrous THF and water represent better solvents for pyrrolidine synthesis than wet THF (see the [Supporting Information](#)). The possibility of using aqueous media is interesting in the context of green chemistry in addition to the advantageous sustainability profile already provided by the use of CO as an atom-economical reductant.⁵ Another important advantage of Ru-based methodology of pyrrolidine synthesis is associated with the fact that the average cost of ruthenium is over 10-fold lower than the cost of rhodium.¹⁰

With these results in hand, we explored the substrate scope of pyrrolidine synthesis (Figure 1). A number of adducts of

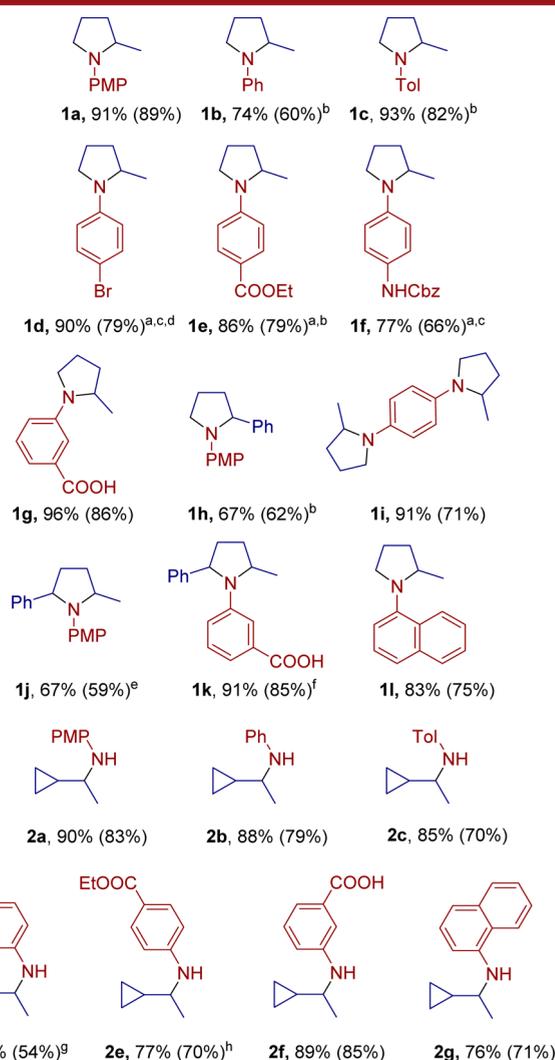


Figure 1. Investigation of the substrate scope for the preparation of pyrrolidines and cyclopropylamines from cyclopropyl ketones. Yields were determined by ¹H NMR with internal standard. Isolated yields are shown in parentheses. For pyrrolidine synthesis: 1.0 mmol of amine, 1.5 mmol of ketone (for each amino group), 1 mol % of RuCl₃ (to each amino group), water, 30 bar CO, 160 °C, 22 h. For cyclopropylamine synthesis: 1.0 mmol of amine, 1.5 mmol of ketone, 2 mol % of Rh₂(OAc)₄, dioxane, 30 bar CO, 130 °C, 24 h. (a) THF was used as solvent. (b) 2 mol % of RuCl₃. (c) 4 mol % of RuCl₃. (d) 110 °C. (e) dr 2.5:1. (f) dr 1.4:1. (g) 110 °C, 48 h. (h) 160 °C, 48 h.

methyl cyclopropyl ketone with different amines were obtained with good to excellent yields (1a–g,i,l). No substantial influence of electronic properties of the aniline substituents was observed: *p*-methoxy-, *p*-methyl-, *p*-bromo-, *p*-ethoxycarbonyl-, and *m*-hydroxycarbonyl-substituted derivatives were obtained in similar yields (83–96%). In addition to aliphatic ketones, the reaction worked equally well for aromatic counterparts (1h), among which D–A cyclopropanes have been successfully employed (1j,k). The protocol exclusively furnished 2,5-disubstituted pyrrolidines when 1,2-disubstituted cyclopropanes were used as starting materials, and no other isomeric pyrrolidines were detected. The methodology could be successfully applied to diamines (1i), which in the broader

context can be useful for the synthesis of bidentate ligands. The reaction was scaled up to 2 mmol without any erosion of the yield (see the [Supporting Information](#)).

Likewise, a useful preparative profile was observed for the Rh-catalyzed protocol. Various products **2a–g** were successfully isolated in good yields ([Figure 1](#)).

Investigation of the mechanistic details of the described processes is beyond the scope of this paper. However, schemes of possible mechanisms are provided in the [Supporting Information](#).

In summary, we have developed highly efficient orthogonal methodologies for a novel one-step preparation of pyrrolidines or traditional preparation of cyclopropyl-substituted amines via reductive amination; the direction of the process can be altered by simply changing the catalyst from ruthenium trichloride to rhodium acetate. The reactions do not require an external hydrogen source or any ligands and employ the unique properties of carbon monoxide as a deoxygenative agent, which renders our methodologies more atom-economical in comparison to the existing synthetic alternatives.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the [ACS Publications website](#) at DOI: [10.1021/acs.orglett.6b02945](https://doi.org/10.1021/acs.orglett.6b02945).

Detailed experimental procedures and full spectroscopic data for all new compounds ([PDF](#))

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was financially supported by the Russian Science Foundation (Grant No. 16-13-10393). We gratefully acknowledge Dr. Rinat Salikov for the cyclopropyl starting materials.

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