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Authors: Ganesh Kumar Thota, Gui-Jun Sun, Tao Deng, Yi Li, and Qiang Kang

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Enantioselective Conjugate Addition of 2-Acylimidazoles with Nitroalkenes Promoted by Chiral-at-Metal Rhodium(III) Complexes

Ganesh Kumar Thota,[†a] Gui-Jun Sun,[†a] Tao Deng,[b] Yi Li,[b] and Qiang Kang[a,*]

[a] Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Center for Excellence in Molecular Synthesis, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, 155 Yangqiao Road West, Fuzhou, 350002, P. R. China
[Fax: (+86)-591-63173548; phone: (+86)-591-63173548; e-mail: kangq@fjirsm.ac.cn]
[b] Department of Chemistry, Fuzhou University, 350116, P. R. China

[†] These authors contributed equally to this work.

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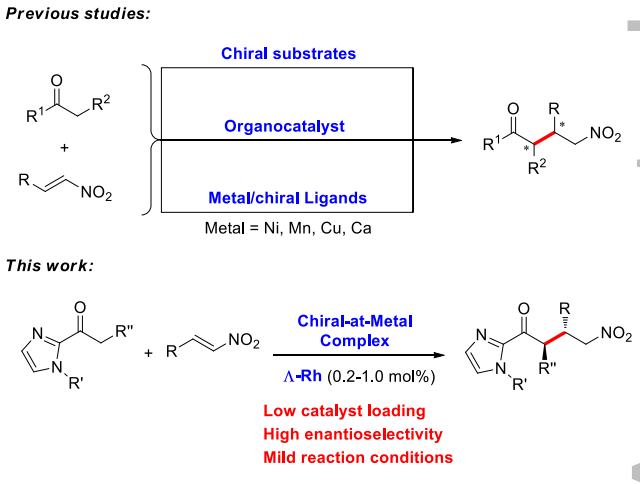
Abstract. An enantioselective conjugate addition of 2-acylimidazoles with nitroalkenes catalyzed by chiral-at-metal rhodium(III) complex under mild reaction conditions was developed, affording versatile *γ*-nitro ketone skeletons in good yields with excellent enantioselectivities (up to >99% ee).

Keywords: Rhodium catalysis; Conjugate addition; Enantioselective; Chiral-at-metal Complex

Nitroalkanes are highly versatile synthetic intermediates on account of their facile *α*-alkylation reactions and interconversions to other important functional groups by various possible transformations.[1] Therefore, catalytic diastereo- and enantioselective conjugate additions of carbon pronucleophiles to nitroalkenes has attracted much attention.[2-4] The substrate-controlled enantioselective Michael additions of ketones to nitroalkenes have been intensively investigated before the emergence of organocatalysts.[2] Since the pioneering contributions from List[5] and Barbas,[6] *L*-proline catalyzed organocatalysis has represented a convenient approach for the asymmetric addition of ketones to nitroalkenes. However, this catalytic system is limited by a relatively large catalyst loading (usually 10-20 mol%) and a long reaction time. Complementarily, organometal complexes have been recognized as attractive catalysts and received continuous and ever-growing attention in this research area during the last decade.[4] The combination of chiral diamine ligands with a metal such as Ni, Ca, Cu and Mn has been well investigated in asymmetric conjugate addition with nitroalkenes. In comparison with the most studied 1,2-[7] and 1,3-dicarbonyl[8] types of nucleophiles, the reaction of nitroalkenes with simple *α*-ketone nucleophiles has not been studied as extensively.[9] In spite of these notable advances, highly efficient protocols for the enantioselective conjugate addition of simple ketones with nitroalkenes are still desirable. On the basis of our recent work on chiral-at-metal catalysts,[10] herein, we disclose the catalytic asymmetric Michael addition of imidazole-modified ketones with nitroalkenes catalyzed by a chiral-at-metal Rh(III) complex with as low as 1 mol% of catalyst loading.[11,12]



Scheme 1. Previous protocols and this work on asymmetric conjugate addition of carbon pronucleophiles to nitroalkenes.

We began the initial optimization studies by evaluating chiral-at-metal Rh(III) complexes in the conjugate addition of *N*-methylimidazole modified ketone **1a** with nitrostyrene **2a**. To our delight, in the presence of 1 mol% of **Λ-Rh1**, the reaction was completed within 17 h, giving the corresponding product **3a** in 95% yield with 89% ee (Table 1, entry

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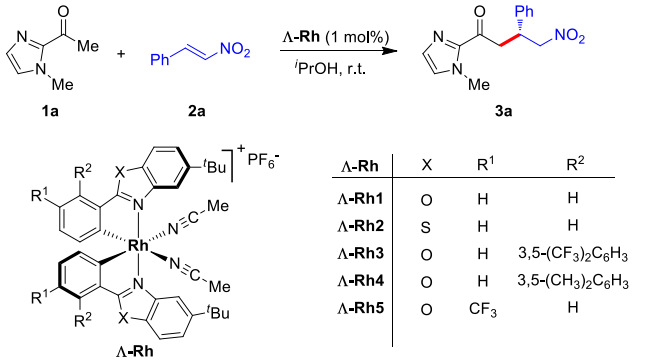
1). Encouraged by these interesting results, we examined different chiral chiral Rh(III) complexes **Λ-Rh2**, **Λ-Rh3**, **Λ-Rh4** and **Λ-Rh5** in the title reaction. Gratifyingly, **Λ-Rh3** was the most effective one among various R^1- and R^2-substituted chiral Rh(III) complexes, probably due to the steric hindrance and electronic effect of 3,5-$(CF_3)_2$-phenyl substitution (entry 3). Further optimization of reaction conditions disclosed that ^{t}BuOH was the best solvent for the title reaction (entry 6, for more details see Supporting Information, Table S2).

Table 1. Optimization of reaction conditions[a]

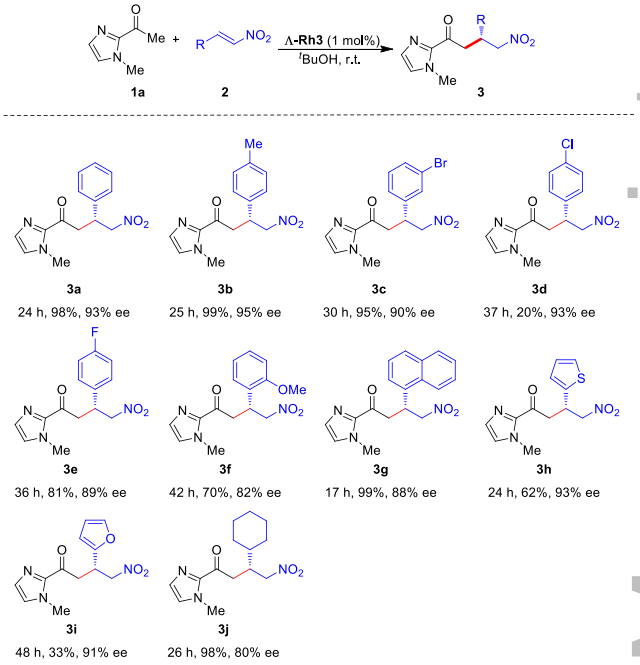


Λ-Rh	X	R^1	R^2
Λ-Rh1	O	H	H
Λ-Rh2	S	H	H
Λ-Rh3	O	H	3,5-$(CF_3)_2C_6H_3$
Λ-Rh4	O	H	3,5-$(CH_3)_2C_6H_3$
Λ-Rh5	O	CF_3	H

Entry	Catalyst	Time [h]	Yield [%][b]	ee [%][c]
1	**Λ-Rh1**	17	95	89
2	**Λ-Rh2**	24	70	86
3	**Λ-Rh3**	24	95	91
4	**Λ-Rh4**	48	80	85
5	**Λ-Rh5**	24	68	84
6[d]	**Λ-Rh3**	24	98	93

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), **Λ-Rh** (1 mol%), ^{i}PrOH (0.3 mL).
[b] Yields were determined by ^{1}H NMR with CH_2Br_2 as an internal standard
[c] Determined by HPLC analysis.
[d] ^{t}BuOH as solvent.

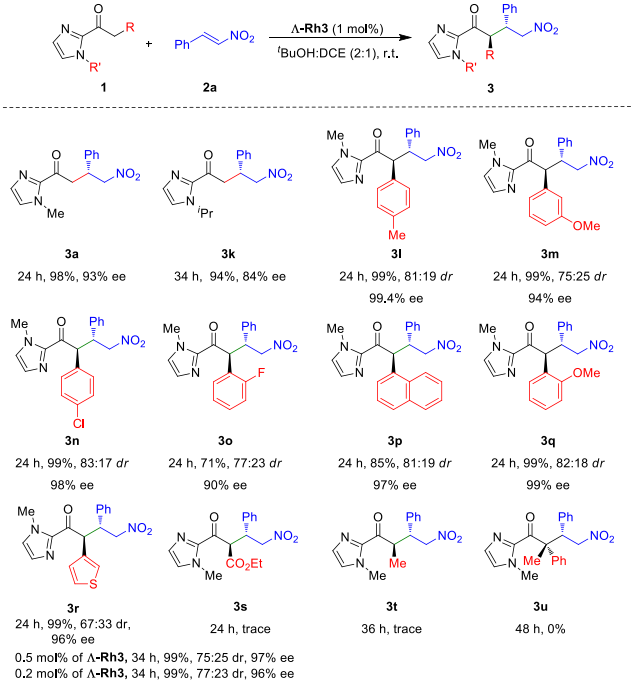
With the optimized reaction conditions in hand (Table 1, entry 6), the substrate scope of various nitroalkenes was examined. As demonstrated in Scheme 2, aromatic nitroalkenes with electron-donating groups (**2a**, **2b**) as well as electron-withdrawing groups (**2c-2e**) in the *para* or *meta* position of the phenyl ring, affording the desired products in good yields with excellent enantioselectivities under the optimal reaction conditions, albeit diminished yield for *para*-Cl substituted nitroalkene **2d**. *ortho*-Substituted aromatic alkene **2f** required a slightly longer reaction time and led to a relatively lower enantioselectivity (82% ee). Moreover, naphthyl substituted nitroalkene (**2g**) gave quantitative yield with high ee value. Interestingly, heteroaryl substituted nitroalkenes (**2h**, **2i**) were also tolerated under the optimal reaction conditions to yield the corresponding products in moderate yields with excellent enantioselectivities. Surprisingly, in addition to aromatic substituents, the aliphatic variants of nitroalkene **2j** also found to be competent partner to provide desired product in 98% yield with diminished enantioselectivity (80% ee).



Scheme 2. Substrate scope of nitroalkenes

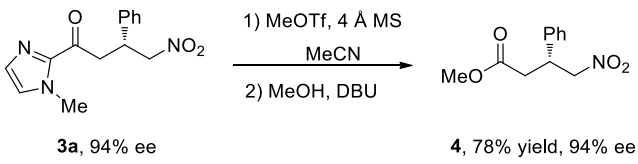
Next, we examined the adaptability of imidazole-modified *α*-ketones (Scheme 3).[13] The bulkiness of the substituent on the imidazole ring (R') has influence on the enantioselectivity, given the fact that sterically hindered isopropyl substituted imidazole delivered desired product **3k** with 84% ee. The electronic nature of the R substituents had limited impact on the reactivity and enantioselectivity, which generated the desired adducts **3l-3n** in quantitative yields with excellent ee (94-99.4% ee). The *ortho*-substituted substrates were also compatible to afford the corresponding products **3o-3q** in 71-99% yields with 90-99% ee. Furthermore, 3-thienyl substituted ketone could also be used for the title reaction to afford the desired product **3r** in 99% yield with 96% ee, albeit with moderate diastereoselectivity. Unfortunately, aliphatic variants of 2-acylimidazoles were not applicable in this transformation, probably due to low nucleophilicity of those substrates. Another limitation is the challenging all-carbon quaternary centres could not be constructed under current protocol (**3u**, 0% yield).[14] Remarkably, the asymmetric conjugate addition of **1r** with **2a** was completed within 34 h in the presence of as low as 0.2 mol% **Λ-Rh3** complex as

catalyst, affording **3r** in 99% yield (495 catalyst turnovers) with 96% ee. The absolute configuration of product **3c** was determined by a single-crystal X-ray analysis (for details, see Supporting Information).[15]



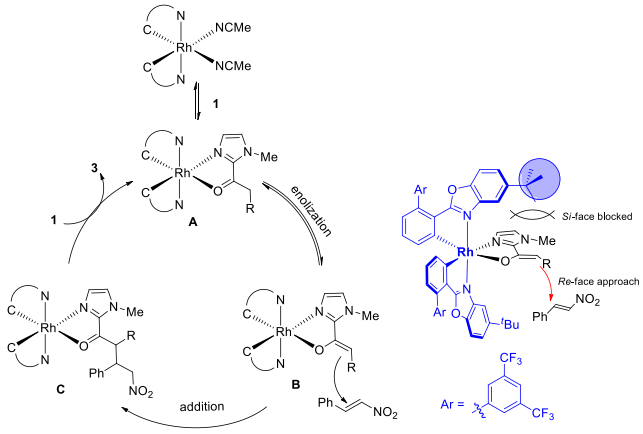
Scheme 3. Substrate scope of imidazole-modified ketones

To illustrate the potential synthetic application of current protocol, further transformation of product to useful synthetic building blocks was carried on. The conjugate adduct **3a** could be easily transferred to corresponding methoxy ester **4** after cleavage of the *N*-methylimidazole group without loss in enantiomeric excess (Scheme 4, **4**, 78% yield, 94% ee).



Scheme 4. Synthetic transformation of product **3a.**

A possible mechanism for chiral-at-metal Rh(III) complex catalyzed enantioselective conjugate addition reaction of imidazole-modified ketones with nitroalkenes is proposed (Scheme 5). Mechanistically, the chiral Rh(III) complex would activate the 2-acylimidazoles **1** through ligand exchange and bidentate *N,O*-coordination (intermediate **A**) followed by deprotonation to generate the enolate (intermediate **B**), which react with nitroalkenes **2** to give intermediate **C**. Ligand exchange of intermediate **C** with **1** delivers the corresponding product **3** followed by initiation of new catalytic cycle. The stereochemistry of the product could be rationalized by approach of the nitroalkene **2** from the less hindered *Re*-face of the enolate according to steric shielding.



Scheme 5. Proposed mechanism

In conclusion, we have developed a highly efficient enantioselective conjugate addition of imidazole-modified ketones with readily available nitroalkenes catalyzed by a chiral-at-metal Rh(III) complex, affording versatile *γ*-nitro ketone skeletons in good yields with excellent enantioselectivities. The reaction was applicable to various substrates and proceeded well in mild reaction conditions. Notably, this protocol exhibits excellent reactivity and enantioselectivity, as the fact that by employing as low as 0.2 mol% **Λ-Rh3** complex, the reaction could be complete with high yield and excellent ee value. Further research on the design new type of chiral Rh(III) complexes and its application in asymmetric synthesis is ongoing in our laboratory.

Experimental Section

General Procedure for Catalytic Enantioselective Michael Addition of 2-Acylimidazoles to Nitroalkenes

To a solution of 2-acyl imidazole substrate **1** (0.2 mmol) in ^{t}BuOH (0.2 mL) or ^{t}BuOH:DCE (2:1, 0.3 mL), 1 mol% of **Λ-Rh3** was added under argon atmosphere. The reaction mixture was allowed to stir at RT for 20 minutes before adding nitroalkenes **2** (1.2 equiv). Then the reaction mixture was allowed to stir at room temperature under argon atmosphere. After the reaction was complete as monitored by TLC, aqueous saturated NH_4Cl (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (3×2 mL). The combined organic layers were washed with brine (4 mL), separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, EtOAc/PE, 1:20) to afford the desired product **3**.

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[15] CCDC 1581350 contains 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.

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