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Nickel-Catalyzed Favorskii-Type Rearrangement of Cyclobutanone Oxime Esters to Cyclopropanecarbonitriles

Bin Shuai
Ping Fang*
Tian-Sheng Mei*

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, P. R. of China
mei7900@sioc.ac.cn
pfang@sioc.ac.cn

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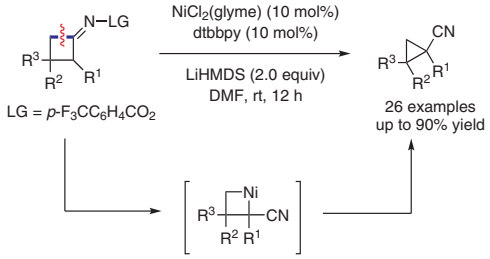

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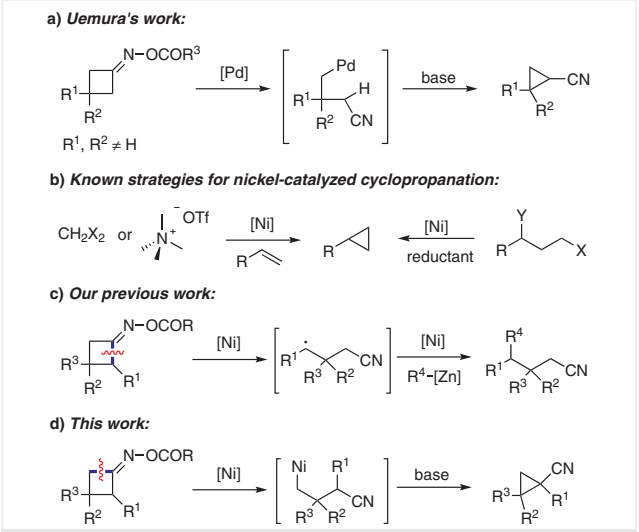
Abstract A nickel-catalyzed base-promoted rearrangement of cyclobutanone oxime esters to cyclopropanecarbonitriles was developed. The ring opening of cyclobutanone oxime esters occurs at the sterically less hindered side. A base-promoted nickelacyclobutane intermediate, formed in situ, is assumed to be involved in the formation of the product.

Key words nickel catalysis, cyclobutanone oxime esters, cyclopropanecarbonitriles, ring opening, Favorskii rearrangement

The cleavage and reorganization of C–C bonds is an important transformation in organic synthesis, and the past two decades have witnessed great advances in this field.[1] Most of the research reported to date relies on a strain-release strategy to achieve C–C bond scission, and therefore small rings are required.[2] The strain release associated with ring cleavage serves as the driving force. Consequently, the reorganization of C–C bonds to form smaller rings is less well developed, primarily because the formation of three- or four-membered rings is thermodynamically unfavorable. As a result of the pioneering work of Zard and co-workers,[3] cyclobutanone oximes and other derivatives have been extensively studied.[4] As redox-active precursors, cyclobutanone oximes can be activated by photocatalysts or transition metals to afford iminyl radicals that subsequently deliver the corresponding alkyl radicals by β-scission of C–C bonds.[5,6] Capture of the alkyl radicals by unsaturated systems or organometallic intermediates provides powerful and efficient methods for constructing valuable nitrile groups, which are present in many pharmaceuticals and agrochemicals. In those transformations, the strained cyclobutanone skeleton is converted into a linear strain-free alkyl nitrile moiety.

In 2000, Uemura and co-workers found that unsaturated nitriles can be obtained from oxime esters by using palladium as a catalyst.[7] In the case of 3,3-disubstituted oxime esters, which have no β-H atoms, a cyclopropane nitrile is obtained (Scheme 1a). The formation of the strained cyclopropane product was rationalized in terms of the formation of a palladacyclobutane intermediate. This type of intramolecular C–H bond activation to form a palladacyclobutane intermediate has also been reported elsewhere,[8] although the scope was limited to substrates lacking a β-H atom. Other catalytic system that used rhodium to activate cyclic ketones to form rings smaller by one carbon atom have also been reported.[9]

Recently, we disclosed a nickel-catalyzed Negishi coupling of cyclobutanone oxime esters with aryl- or alkylzinc reagents (Scheme1c) in which ring opening occurs at the



Scheme 1 Metal-catalyzed ring opening and cyclopropanation reactions

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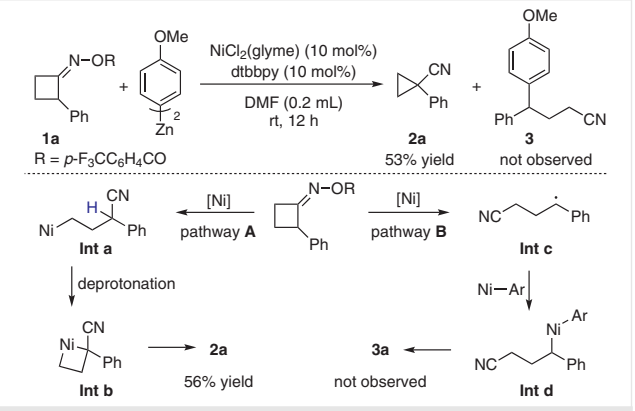
sterically hindered site.[10] In the reaction, the alkyl radical that is formed is trapped by a nickel species to deliver the corresponding acyclic nitrile. As a part of our continuing interest in nickel catalysis and redox-active species, we found that in the presence of base, cyclobutanone oxime esters can be converted into more-strained cyclopropane derivatives. Strategies for cyclopropane formation under nickel catalysis are rare and can be divided into two categories (Scheme 1b): nickel-catalyzed Simmons–Smith-type cyclopropanation and nickel-catalyzed intramolecular reductive cross coupling.[11,12] Here, we report a new strategy to prepare cyclopropane nitriles by using cyclobutanone oxime esters as starting materials.

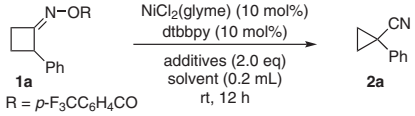
Initially, we attempted to extend our previous work to the synthesis of the 1,1-diaryl product **3** from the 2-phenylcyclobutanone oxime ester **1a** (Scheme 2). Surprisingly, we did not observe the desired product **3** and, instead, the cyclopropanecarbonitrile **2a** was obtained in 53% yield (Scheme 2). This intriguing result prompted us to consider the possible reaction pathway and the role of the arylzinc reagent in the reaction. As shown in Scheme 2, oxime ester **1a** is activated by the nickel catalyst to form an alkylnickel intermediate **Int a**, which undergoes deprotonation at the α-H atom ($pK_a \approx 22$ in DMSO) to afford the cyclic intermediate **Int b**; this, in turn, undergoes reductive elimination to give product **2a**. The arylzinc compound is assumed to serve as a base rather than an arylation reagent.



Scheme 2 A possible reaction pathway for the formation of **2a**; [$NiCl_2$(glyme)] = nickel(II) chloride–ethylene glycol dimethyl ether complex; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine

On the basis of this hypothesis, we surmised that the ease of removal of the acidic α-H of **Int a** was critical for the reaction, and we examined the effects of various bases (Table 1). In the absence of the [$NiCl_2$(glyme)] catalyst and dtbbpy ligand, no product was observed (Table 1, entry 2). Ethyl- and methylzinc reagents and trimethylaluminum gave none of the desired product (entries 3–5). However, methyl and phenyl Grignard reagent afforded nitrile **2a** in yields of 28 and 21%, respectively (entries 6 and 7). Pleasingly, the yield of **2a** doubled when sodium *tert*-butoxide was used as an additive, and the yield improved dramatically to 90% on using the stronger base LiHMDS (entry 9). NaHMDS and KHMDS, however, gave inferior result (entries 10 and 11), suggesting that the lithium cation has a beneficial effect on the reaction.[13] The solvent also plays an important role in this reaction. The yield slightly decreased when THF was used as the solvent (entry 12), and the use of the polar solvents MeCN and NMP resulted in severe decreases in the product yield (entries 13 and 14). Attempts to lower the catalyst loading from 10 to 5 mmol% also led to an inferior yield (entry 15). We also evaluated the possibility of using a smaller amount of LiHMDS (entry 16), but the yield dropped to 62%, indicating that LiHMDS not only serves as a base, but might also be responsible for catalyst activation.

Table 1 Optimization of the Reaction Conditions[a]

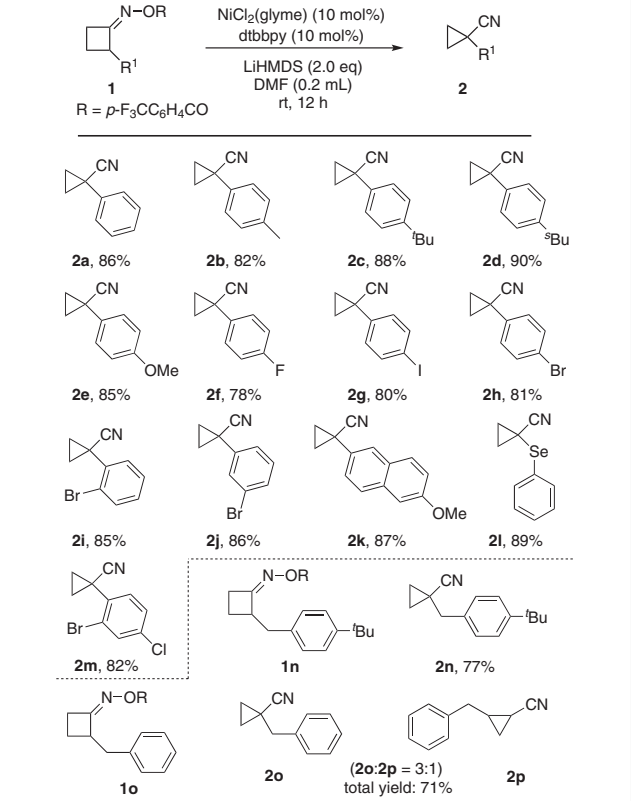


Entry	Additive	Solvent	Yield[b] (%)
1	$(p\text{-MeOC}_6H_4)_2Zn$	DMF	53%
2[c]	$(p\text{-MeOC}_6H_4)_2Zn$	DMF	NR
3	Et_2Zn	DMF	NR
4	Me_2Zn	DMF	NR
5	Me_3Al	DMF	NR
6	MeMgBr	DMF	28
7	PhMgBr	DMF	21
8	*t*-BuONa	DMF	42
9	LiHMDS	DMF	90
10	NaHMDS	DMF	57
11	KHMDS	DMF	85
12	LiHMDS	THF	80
13	LiHMDS	NMP	10
14	LiHMDS	MeCN	15
15[d]	LiHMDS	DMF	71
16[e]	LiHMDS	DMF	62

[a] Reaction conditions: $NiCl_2$(glyme) (10 mol%), dtbbpy (10 mol%), **1a** (0.2 mmol, 1.0 equiv), LiHMDS (0.4 mmol, 2.0 equiv), DMF (0.2 mL), rt, 12 h.
[b] Yield determined by ^1H NMR with 1,4-dimethoxybenzene as internal standard.
[c] No nickel catalyst or dtbbpy.
[d] 5 mol% each of $NiCl_2$(glyme) and dtbbpy were used.
[e] 1.0 equiv of LiHMDS was used.

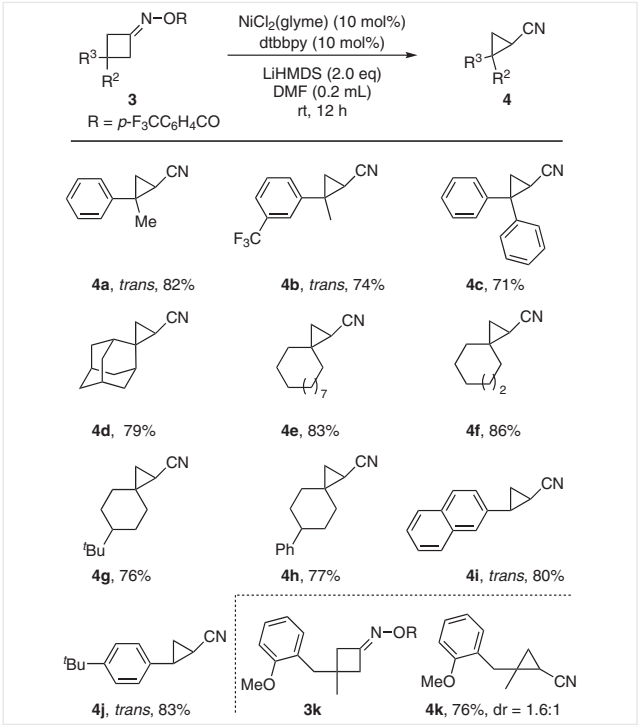
With the optimized conditions in hand, we moved on to investigate the substrate scope of this nickel-catalyzed Favorskii-type rearrangement. A variety of 2-substituted oxime esters were successfully converted into the corresponding cyclopropanecarbonitriles in good yields (Scheme 3). Substrates bearing various electron-donating-groups, such as methyl, *tert*-butyl, *sec*-butyl, or methoxy, reacted

smoothly to afford the desired product **2a–e** and **2k**. More importantly, fluoro, chloro, bromo, and iodo groups were all well tolerated under the standard reaction conditions (**2f–j**, **2m**). A phenylselanyl-group-containing oxime was also investigated and proved to be an efficient substrate (**2l**). Interestingly, when oxime **1n** was used as substrate, nitrile **2n** was isolated in 77% yield, whereas oxime **1o** afforded a 3:1 mixture of **2o** and **2p**. A five-membered substrate, the corresponding 2-phenylcyclopentanone oxime ester, decomposed under the standard conditions and delivered none of the desired product.



Scheme 3 Substrate scope for 2-substituted oxime esters. Isolated yields are reported.

Our success in using oxime **1n** as a substrate encouraged us to extend this method to the rearrangement of 3-substituted oxime esters. To our delight, oxime esters **1** with various functional groups delivered the corresponding nitriles **2** in good yields (Scheme 4). For aryl-substituted oximes, the corresponding cyclopropanecarbonitriles were obtained with a *trans*-configuration, as determined by NOESY studies. However, for substrate **3k** with two alkyl groups, the product **4k** was formed with low diastereoselectivity. The difference in selectivity between aryl and alkyl groups might arise from steric hindrance. The aryl group is bulky

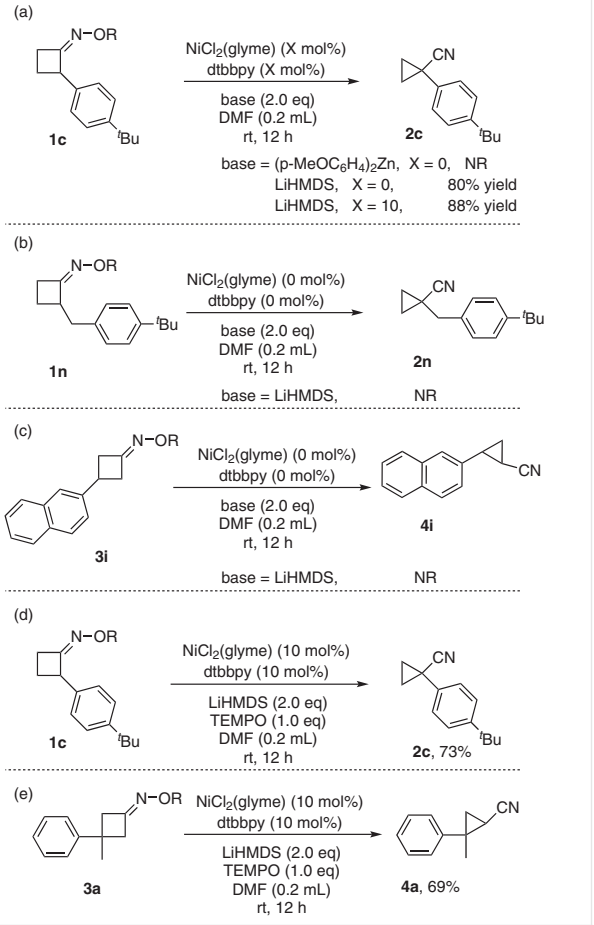


Scheme 4 Substrate scope for 3-substituted oxime esters. Isolated yields are reported.

and the nickelcyclobutane intermediate is more stable when the aryl and cyano group adopt a *trans*-configuration.

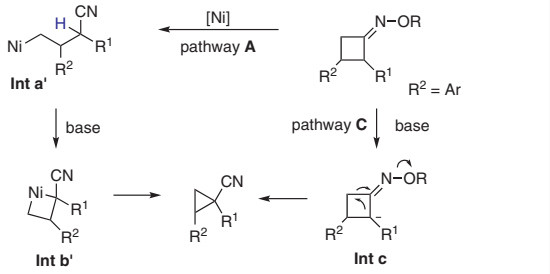
To gain insights into the reaction mechanism, we performed some control experiments. For 2-aryl-substituted oxime esters in the presence of a weak base, nickel is necessary for product formation. However, when the base was sufficiently strong (for example, LiHMDS), the product formed in 80% yield in the absence of a nickel catalyst; addition of nickel resulted in a slight improvement of the yield to 88% (Scheme 5a). For 2-alkyl and 3-substituted oxime esters, no product was observed in the absence of the nickel catalyst (Schemes 5b and 5c). This indicates that the putative reaction pathway shown in Scheme 2 is responsible for product formation in the presence of a weak base but is not a major pathway when a strong base is used. When oxime ester **1c** or **3a** reacted under the standard conditions in the presence of a stoichiometric amount of TEMPO, the corresponding products **2c** and **4a** were isolated in yields of 73% and 69%, respectively (Schemes 5d and 5e). No radical-trapping product was observed, suggesting that radical formation was not involved in product formation.

On the basis of the above results, we propose that in the presence of a weak base, the product is formed by Pathway A (Scheme 6), whereas in the presence of a strong base, the proton in the α-position of the 2-aryl oxime esters can be deprotonated to form an anion (Pathway C). A Favorskii-type rearrangement then occurs to deliver the product. At



Scheme 5 Control experiments

the same time, Pathway A might make a small contribution to product formation. For 2-alkyl and 3-substituted substrates, the base was not strong enough to remove the α-H atom of the oxime, so the nickel-catalyzed Pathway A is responsible for product formation.



Scheme 6 Proposed reaction mechanism

In conclusion, we have developed a nickel-catalyzed Favorskii-type rearrangement of cyclobutanone oxime esters.[14] In the reaction, C–C bond cleavage occurs at the sterically less hindered side, which represents complementary reactivity with respect to previous work. Preliminary mechanistic experiments suggest that no radical species are involved in the product formation.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690872.

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(14) **Cyclopropanecarbonitriles 2; General Procedure**
In a glove box, a 4 mL screw-capped vial was charged with the appropriate oxime ester **1** (0.2 mmol), $NiCl_2$(glyme) (4 mg, 0.02 mmol), dtbbpy (5 mg, 0.02 mmol), and DMF (0.2 mL). The mixture was then stirred for 15 min at rt, and a 1.0 M solution of LiHMDS in THF (0.4 mL, 0.4 mmol) was added. The vial was removed from the glove box, and the mixture was stirred at rt for 12 h. The reaction was then quenched with 1 N sat. aq NH_4Cl and diluted with EtOAc. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under a vacuum. The product was then obtained by flash chromatography.

1-(4-*sec*-Butylphenyl)cyclopropanecarbonitrile (**2d**)
Yellow oil; yield: 35.85 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.2 Hz, 2 H), 7.12 (d, *J* = 8.3 Hz, 2 H), 2.45 (d, *J* = 7.2 Hz, 2 H), 1.84 (dt, *J* = 13.5, 6.7 Hz, 1 H), 1.72–1.66 (m, 2 H), 1.41–1.34 (m, 2 H), 0.89 (d, *J* = 6.6 Hz, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.29, 133.20, 129.59, 125.59, 122.82, 44.87, 30.17, 22.29, 17.93, 13.50. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_{17}N$: 199.1356; found: 199.1355.

1-(Phenylselanyl)cyclopropanecarbonitrile (**2l**)
Yellow oil; yield: 39.69 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.61 (m, 2 H), 7.38 (dd, *J* = 5.0, 1.9 Hz, 3 H), 1.74–1.67 (m, 2 H), 1.41–1.35 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 133.74, 129.58, 128.82, 128.27, 122.70, 18.31, 2.62. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_9N^{80}Se$: 222.9895; found: 222.9894.