Nickel-Catalyzed Cascade Annulation for the Rapid Synthesis of Carbocyclic Nitriles

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Dedicated to François Diederich

We report a Ni-catalyzed cascade annulation reaction that proceeds through two sequential carbometallation steps followed by C-CN reductive elimination. This reaction transforms two simple starting materials into complex, carbocyclic nitriles.

Keywords: Nitrile • Nickel • Alkyne • Alkene • Annulation

Introduction

The reversible oxidative addition of C-CN bonds has recently emerged as a powerful tool for the rapid synthesis of synthetically useful nitriles. Most notably, Nakao and Hiyama have disclosed a Ni-catalyzed alkyne insertion reaction into C-CN bonds that can be used for the atom-economical synthesis of vinyl nitriles. Inspired by this unique reactivity, our group has developed a host of transformations that rely on the reversibility of the C-CN oxidative addition step. This includes both nickel-catalyzed transfer hydrocyanation and aryl cyanation reactions that elude the need for toxic cyanide-based reagents such as HCN or KCN. Furthermore, we have employed a similar strategy for the development of a cascade carbometallation-Heck sequence which provided direct access to annulated alkene products upon loss of the cyano group. In this communication, we report a related catalytic reaction that retains the cyano group in the final product, leading to the rapid synthesis of complex carbocyclic nitriles through the concomitant formation of three new C-C bonds.

Results and Discussion

Based on our previously developed Heck-type annihilation reaction and inspired by seminal literature examples of cascade carbohalogenation reactions developed by Lautens and Tong, we reasoned that the use of styrenyl cyanide substrates bearing a 1,1-disubstituted alkene would prevent any β-hydride elimination, allowing for the incorporation of the valuable nitrile group into the final product after C-CN reductive elimination. Optimization of a model reaction (Table 1) revealed that a simple catalyst system composed of Ni(COD)₂ and PPh₃ worked best for the synthesis of the desired product 3aa in good yields. The temperature could be decreased to a mild 50°C after further optimization (Entry 20). Similar to our previous studies in this area, the use of AlMe₂Cl as a Lewis acid was critical for this reaction to proceed. We surmise that the Lewis acid lowers the barrier for the challenging C-CN oxidative addition and reductive elimination.

Table 1. Evaluation and Optimization of Reaction Conditions

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<th>Temperature /°C</th>
<th>Yield 3aa/%</th>
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Scheme 1. Context of the work.

Previous work (ref. 4 and 5c):

This work:
Table 2. Substrate Scope

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*Reaction conditions: 1a (71.6 mg, 0.5 mmol), 2a (55.1 mg, 0.5 mmol), 1.0M AlMe2Cl in hexane (0.10 mL, 0.10 mmol), Ni(COD)2 (6.9 mg, 5 mol%, 25 μmol), monodentate ligand (10 mol%, 50 μmol) or bidentate ligand (5 mol%, 25 μmol) in toluene (1 mL) at 100 °C for 16 hours. GC yield using n-dodecane (100 μL) as internal standard. Without Ni(COD)2. Ni(COD)2 (2.75 mg, 2 mol%, 10 μmol), PPh3 (5.24 mg, 4 mol%, 20 μmol) and 1.0M solution of AlMe2Cl in hexane (40 μL, 40 μmol).

Having identified suitable conditions for this transformation, we explored the scope of the reaction with regards to the styrenyl component (Table 2). Halogen (3ba 3da), acetal (3ca), ether (3ea) substituents were well tolerated, while amino and nitro groups did not give any conversion to the desired product. A thiophene substrate successfully cyclized to form an interesting heterocyclic motif (3fa).

We then looked at the other component of the reaction. Cyclododecyne readily participated to give tricyclic product 3ac. While aliphatic alkenes were generally unreactive, norbornene provided the desired tetracyclic product in good yield as a mixture of diastereoisomers (3ad). Gratifyingly, non-symmetrical, silyl-substituted alkenes reacted with high regioselectivity, leading to the formation of valuable synthetic building blocks (3aea and 3af). Finally, diarylalkynes (3ag) can also be employed as reaction partners when the reaction temperature is increased to 80 °C.

**Conclusion**

In conclusion, we have developed a Ni-catalyzed cascade annulation reaction that proceeds through two sequential carboligation steps followed by C-CN reductive elimination. The reaction is initiated by a
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Lewis-acid assisted C–CN oxidative addition and can transform two simple starting materials into complex, carbocyclic nitriles. Overall, this reaction provides a versatile new route to complex nitrile building blocks which are sought after intermediates in organic synthesis.

Supplementary Material ((optional))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number. ((Please delete this text if not appropriate))

Acknowledgements ((optional))

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Author Contribution Statement

XF, PY and BM designed the reaction. XF, PY and SW performed the experiments. BM wrote the manuscript with inputs from all authors.

References


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Entry for the Table of Contents

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