

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

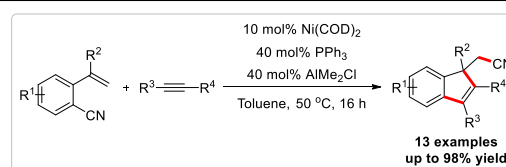
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Dedicated to François Diederich

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.

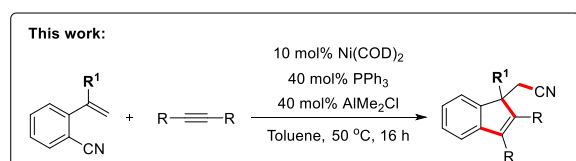
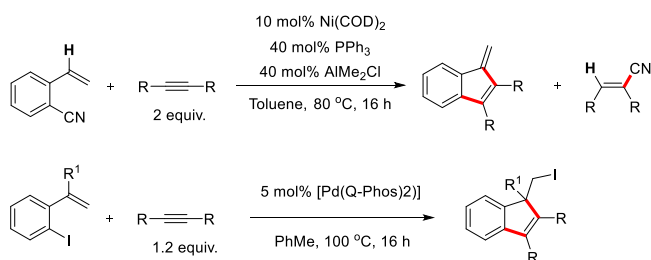
Keywords: Nitrile • Nickel • Alkyne • Alkene • Annulation



Introduction

The reversible oxidative addition of C–CN bonds has recently emerged as a powerful tool for the rapid synthesis of synthetically useful nitriles.^[1–4] 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.^[5–21] 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.^[22–27] 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 a direct access to annulated alkene products upon loss of the cyano group.^[28] In this communication, we report a related catalytic reaction that *retains* the cyanide group in the

Previous work (ref. 4 and 5c):



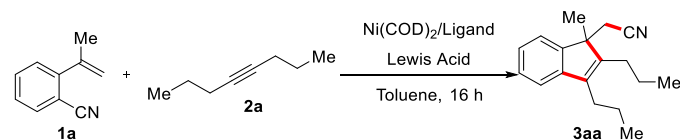
Scheme 1. Context of the work.

final product, leading to the rapid synthesis of complex carbocyclic nitriles through the concomitant formation of three new C–C bonds.

Results and Discussion

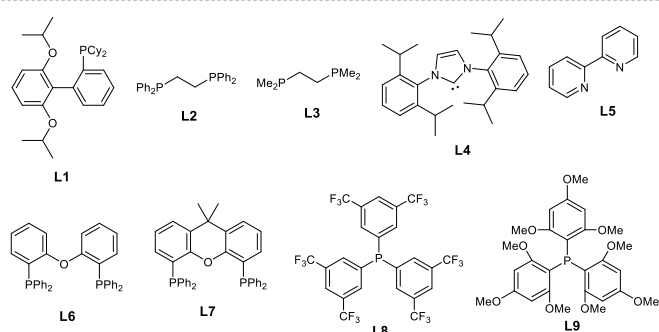
Based on our previously developed Heck-type annulation reaction and inspired by seminal literature examples of cascade carbohalogenation reactions developed by Lautens and Tong,^[29–39] we reasoned that the use of styrenyl cyanide substrates bearing a 1,1-disubstituted alkene would prevent any β -hydride 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^a



Entry	Ligand	Lewis Acid	Temperature /°C	Yield 3aa /% ^b
1	PEt ₃	-	100	Trace
2	PEt ₃	AlMe ₂ Cl	100	70
3 ^c	PEt ₃	AlMe ₂ Cl	100	0
4	-	AlMe ₂ Cl	100	0
5	PPh ₃	AlMe ₂ Cl	100	86
6	PCy ₃	AlMe ₂ Cl	100	Trace
7	PPhMe ₂	AlMe ₂ Cl	100	78

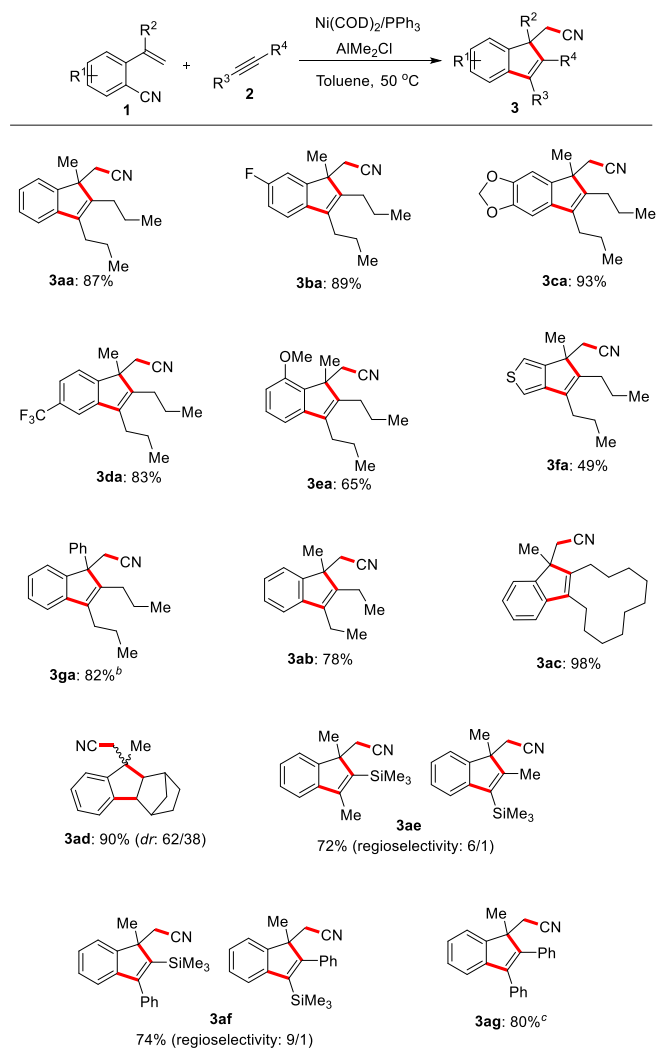
8	L1	AlMe ₂ Cl	100	62
9	L2	AlMe ₂ Cl	100	4
10	L3	AlMe ₂ Cl	100	72
11	L4	AlMe ₂ Cl	100	8
12	L5	AlMe ₂ Cl	100	13
13	L6	AlMe ₂ Cl	100	66
14	L7	AlMe ₂ Cl	100	3
15	L8	AlMe ₂ Cl	100	22
16	L9	AlMe ₂ Cl	100	4
17	PPh ₃	BPh ₃	100	5
18	PPh ₃	B(C ₆ F ₅) ₃	100	5
19	PPh ₃	AlMe ₂ Cl	75	88
20	PPh₃	AlMe₂Cl	50	90
21	PPh ₃	AlMe ₂ Cl	RT	56
22 ^d	PPh ₃	AlMe ₂ Cl	50	10



^aReaction 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. ^bGC yield using *n*-dodecane (100 μL) as internal standard. ^cWithout Ni(COD)₂. ^dNi(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**).

Table 2. Substrate Scope^a



^aReaction conditions: **1** (71.6 mg, 0.5 mmol), **2** (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), PPh₃ (13.1 mg, 10 mol%, 50 μmol) in toluene (1 mL) at 50 °C for 16 hours. ^bAt 100 °C. ^cNi(COD)₂ (10 mol%), PPh₃ (40 mol%) and 1.0M solution of AlMe₂Cl in hexane (0.20 mL, 0.20 mmol), **2g** (1.5 mmol) at 80 °C for 16 hours.

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 alkynes reacted with high regioselectivity, leading to the formation of valuable synthetic building blocks (**3ae** 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 carbometallation steps followed by C–CN reductive elimination. The reaction is initiated by a

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.


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