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Ni-Catalyzed Intramolecular C–O Bond Formation: Synthesis of Cyclic Enol Ethers

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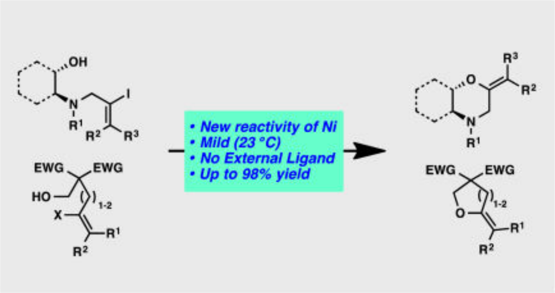
Abstract

An efficient and exceptionally mild intramolecular nickel-catalyzed carbon–oxygen bond-forming reaction between vinyl halides and primary, secondary, and tertiary alcohols has been achieved. Zinc powder was found to be an essential additive for obtaining high catalyst turnover and yields. This operationally simple method allows direct access to cyclic vinyl ethers in high yields in a single step.

Nickel-O–C-eon: It’s child’s play

An unprecedented nickel-catalyzed intramolecular C–O bond forming reaction between aliphatic hydroxyl nucleophiles and tethered vinyl halides is disclosed. The reaction conditions are exceptionally mild, operationally simple, and provide access to various cyclic vinyl ethers in a single step. We believe that exploration of this new reactivity of nickel catalysts can provide further insight into the unique properties and opportunities afforded by nickel catalysts.



Keywords

nickel; C–O bond formation; cross-coupling; vinyl ethers

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Transition metal-catalyzed cross-coupling reactions have served a powerful tool for efficient carbon–carbon and carbon–heteroatom bond formations over the past several decades.[1] Recently, nickel catalysis has emerged in the synthetic community as an exceptionally useful strategy for cross-coupling.[2] Although tremendous advances in nickel-catalyzed carbon–carbon bond formation have been achieved (e.g., Negishi, Suzuki, Stille, Kumada, Hiyama couplings),[3] nickel-catalyzed carbon–oxygen bond forming processes have proven significantly more challenging. The rationale behind this is that reductive elimination of Ni(II) alkoxide complexes is often cited as being significantly challenging even at elevated temperatures.[4] To circumvent this challenge, stoichiometric oxidation of Ni(II) to the less stable Ni(III) analogs has been required. Additionally, reductive elimination of Ni(II) alkoxides is reported to be endothermic via computational analysis. This is in contrast to that of Pd(II) alkoxides, which are exothermic.[5] In 1997, Hartwig and co-workers developed the first nickel-catalyzed cross-coupling between electron-deficient aryl halides and pre-formed sodium alkoxides or sodium siloxides.[6] In 2014, the Ranu group reported a copper-assisted nickel-catalyzed coupling of phenol derivatives and vinyl halides.[7] However, both of these reactions require high temperatures, and the scope of the nucleophiles is limited to pre-formed alkoxides or phenols. Most recently, MacMillan and co-workers developed the nickel-catalyzed intermolecular cross-coupling of aryl bromides and aliphatic alcohols in the presence of light and a photoredox catalyst.[8] Importantly, MacMillan and co-workers could did observe their desired C–O coupling products in the absence of either the photocatalyst or light. Although Pd- or Cu-catalyzed C–O bond forming reactions have been significantly developed, most of these reactions require high temperature that can limit their utility in the synthesis of multifunctional complex molecules. Moreover, the vast majority of these examples are for aryl ether synthesis, not enol ether synthesis.[9, 10, 11] To our knowledge, a mild and efficient nickel-catalyzed intramolecular cross-coupling cyclization between aliphatic hydroxyl nucleophiles and tethered vinyl halides is unprecedented.

In the course of an alkaloid synthesis effort, we attempted a nickel-catalyzed reductive Heck reaction of vinyl iodide **1** with the aim of producing tricycle **2** (Scheme 1, red arrows).[12] Surprisingly, instead of the desired intramolecular C–C bond-forming reaction, a C–O bond-forming cyclization between the vinyl iodide and the free hydroxyl group furnished morpholine derivative **3** (Scheme 1, blue arrows). Given the lack of precedent in the literature for such a transformation with nickel catalysis, we set out to explore the generality of this reaction. Herein, we describe the first nickel-catalyzed cycloetherification of aliphatic alcohols with pendant vinyl halides.

Given this interesting preliminary data, we chose aminocyclohexanols **4a** and **4b** as simplified substrates for reaction optimization studies (Table 1). Our initial reaction conditions afforded the corresponding morpholines **5a** and **5b** in 53% and 42% yield, respectively (entries 1 and 2). A wide variety of bases and additives were investigated to improve the yield and catalytic efficiency (entries 3–10). We found triethylamine to be superior to others examined (entries 3–5). The use of a 1:1 mixture of triethylamine and DABCO allowed etherification in 69% yield with reduced catalyst loading (i.e., 20 mol % $Ni(COD)_2$, entry 6). Gratifyingly, the use of 2 equiv of zinc powder as an additive resulted in a significant improvement in yield (84%) with only 5 mol % of Ni(COD)$_2$ (entry 10).[12, 14, 15, 16, 17]

With optimized conditions in hand, we investigated the substrate scope of the transformation (Table 2). In addition to simple vinyl iodides (e.g., **4b**, R^1 = Me, R^2 = H, R^3 = H),[18] a (*Z*)-styrenyl iodide (i.e., **4c**, R^1 = Me, R^2 = H, R^3 = Ph)[19] furnished vinyl ether **5c** in high yield and without loss of olefin stereochemical fidelity. Aminocyclohexanols bearing isopropyl and allyl substituents on nitrogen afforded the corresponding products in reduced yields (**5d** and **5e**). Electronically variable benzyl groups were compatible under the reaction conditions, and even an aryl bromide was well tolerated (**5f**–**5h**). Additionally, a silyl ether group remained intact, generating substituted morpholine **5i** in good yield. Moreover, we discovered that a *cis*-aminocyclohexanol derived substrate was competant in the reaction, providing the *cis*-fused bicyclic product **5j**.

To our delight, we found that the nickel-catalyzed intramolecular etherification reactions also proceeded with linear aminoalcohol substrates to generate monocyclic morpholine derivatives in moderate to high yields (Table 3). The steric environment of the alcohol fragment did not hinder the performance, as substrates containing primary, secondary, or highly congested tertiary hydroxyl nucleophiles furnished the corresponding cyclic vinyl ethers in excellent yields (**7a**–**7c**). Finally, a benzyl-substituted linear aminoalcohol substrate was transformed to the desired vinyl ether in modest yield (**7d**).

We were pleased to discover that additional acyclic substrates undergo the nickel-catalyzed carbon–oxygen cross-coupling to furnish alkylidene tetrahydrofurans and dihydropyrans (Table 4). Intramolecular etherification of vinyl iodide **8a** furnished the cyclic ether **9a** in good yield in only 1 h (entry 1). Although less reactive, a vinyl bromide also fared well in the reaction, affording the corresponding product in 52% yield after 12 h (entry 2). Unfortunately, attempts to employ a vinyl chloride as the coupling partner led predominantly to recovery of starting material (entry 3). Mono-methyl and mono-phenyl substituted vinyl iodides (**8d** and **8e**)[20] afforded the desired ethers (**9d** and **9e**) in good yields with retention of olefin stereochemistry (entries 4 and 5). Gratifyingly, tetrasubstituted vinyl bromide **8f**[21] furnished the corresponding tetrahydrofuran product **9f** in excellent yield (entry 6). Di-*tert*-butyl and dibenzyl malonates (**8g** and **8h**) were tolerated under the standard reaction conditions to afford the desired ethers (**9g** and **9h**) in good yields (entries 7 and 8). Additionally, carbon–oxygen bond formations were achieved with nitrile- and amide-containing substituents in 61% and 70% yield, respectively (entries 9 and 10). Formation of a six-membered cyclic vinyl ether (**9k**) from substrate **8k** was found to be challenging with only low levels of conversion (entry 11). Interestingly, cycloetherification of **8l** did indeed produce a pyran derivative in good yield, but only isomerized product **9l** was isolated (entry 12).[22]

In conclusion, a highly efficient, mild, and operationally simple nickel-catalyzed intramolecular carbon–oxygen bond-forming reaction between vinyl halides and aliphatic alcohols has been developed. We discovered that zinc powder plays an important role in improving catalyst turnover and isolated yields. The reaction is tolerant of many functional groups, affording various cyclic vinyl ethers in good to excellent yields. This work further expands the capability of nickel catalysis in the context of small molecule chemical synthesis. Additional studies are ongoing to expand the scope of the reaction, to understand the mechanism, and to deploy the cyclization in the context of a complex molecular target.[23] These efforts will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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74:5075–5078. [PubMed: 19476328] Nordmann G, Buchwald SL. J Am Chem Soc. 2003; 125:4978–4979. [PubMed: 12708838] Shade RE, Hyde AM, Olsen JC, Merlic CA. J Am Chem Soc. 2010; 132:1202–1203. [PubMed: 20067245]

11. For an example of a base-mediated intramolecular synthesis of an alkylidene morpholine by C–O bond formation, see: Bottini AT, Mullikin JA, Morris CJ. J Org Chem. 1964; 29:373–379.
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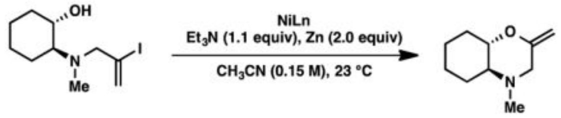
14. Importantly, if the Ni(COD)$_2$ catalyst was omitted, no carbon–oxygen bond formation was observed. Addition of other additives such as Mg and CuI decreased the yields (36% and 0% yield, respectively).
15. Intramolecular etherification of vinyl iodide 4b proceeded with 5 mol % of NiI$_2$ or NiBr$_2$(dme) to furnish vinyl ether 5b (entries 1 and 2). An increased rate of cycloetherification was observed with 10 mol % of NiBr$_2$(dme) (entries 2 and 3). Unfortunately, attempts to convert vinyl iodide 4b to enol ether 5b outside a N$_2$-filled glove box were unsuccessful (entries 4 and 5).



4b **5b**

entry	NiLn	Ni mol %	time	yield (%)[a]
1[b]	NiI$_2$	5	16 h	60
2[b]	NiBr$_2$(dme)	5	48 h	53
3[b]	NiBr$_2$(dme)	10	16 h	51
4[c]	NiI$_2$	5	24 h	0
5[c]	NiBr$_2$(dme)	5	24 h	0

[a] Yield of isolated product.

[b] Reactions were performed in a N$_2$-filled glove box.

[c] Reactions were performed under argon outside a N$_2$-filled glove box.

16. No significant improvement in yield or catalyst turnover was observed when various ligands (e.g., various NHC, PYBOX, BOX, diamine, BiOX ligands) were employed.
17. Since intramolecular etherifications of aminocyclohexanols 4a or 4b proceeded even without Zn powder despite low yields and catalyst turnover (Table 1), we envision that Zn powder likely plays an important role as a scavenger of the forming HI.
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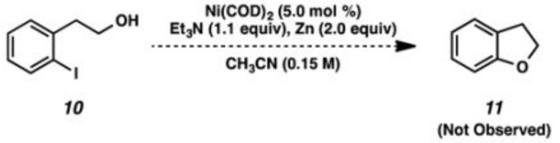
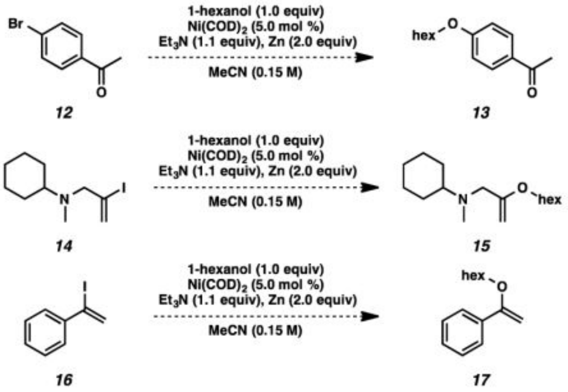
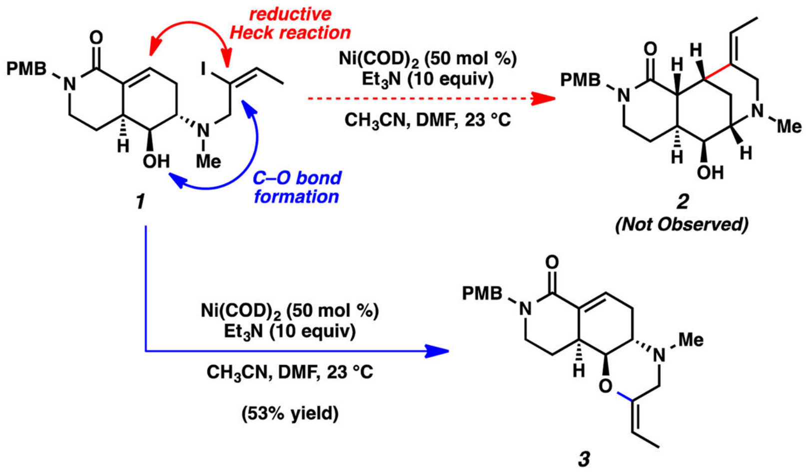
22. Although we attempted to construct 2,3-dihydrobenzofuran 11 from aryl iodide 10 under our standard reaction conditions, only unreacted starting material was recovered.



23. An intermolecular etherification of MacMillan's substrate 12 (ref. 8) with 1-hexanol under our reaction conditions was not successful. Additionally, attempted intermolecular cross-coupling processes of 14 and 16 with 1-hexanol under our standard reaction conditions resulted in no reaction.

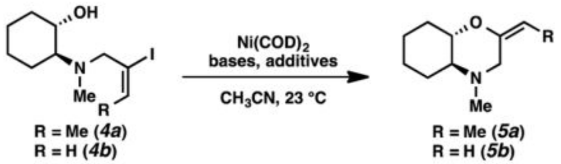




Scheme 1.
Ni-Catalyzed C–O Bond Formation

Table 1

Optimization of Reaction Parameters[a]



entry	substrate	conc(M)	Ni mol %	base	additive	yield (%)[b]
1[c]	**4a**	0.02	50	Et_3N (10 equiv)	–	53
2[c]	**4b**	0.02	50	Et_3N (10 equiv)	–	42
3[c]	**4a**	0.02	35	Et_3N (10 equiv)	–	42[d]
4[c]	**4a**	0.02	35	Cs_2CO_3 (3.0 equiv)	–	30[d]
5[c]	**4a**	0.02	35	K_3PO_4 (3.0 equiv)	–	34[d]
6	**4b**	0.10	20	Et_3N (1.0 equiv)	DABCO (1.0 equiv)	69
7	**4b**	0.10	20	Et_3N (1.0 equiv)	CsF (1.0 equiv)	51
8	**4a**	0.04	20	DABCO (1.0 equiv)	–	24
9	**4a**	0.04	20	DABCO (2.0 equiv)	–	50[d]
10	**4b**	0.15	5	Et_3N (1.1 equiv)	Zn (2.0 equiv)	84

[a] Reactions were performed in a N_2-filled glove box.

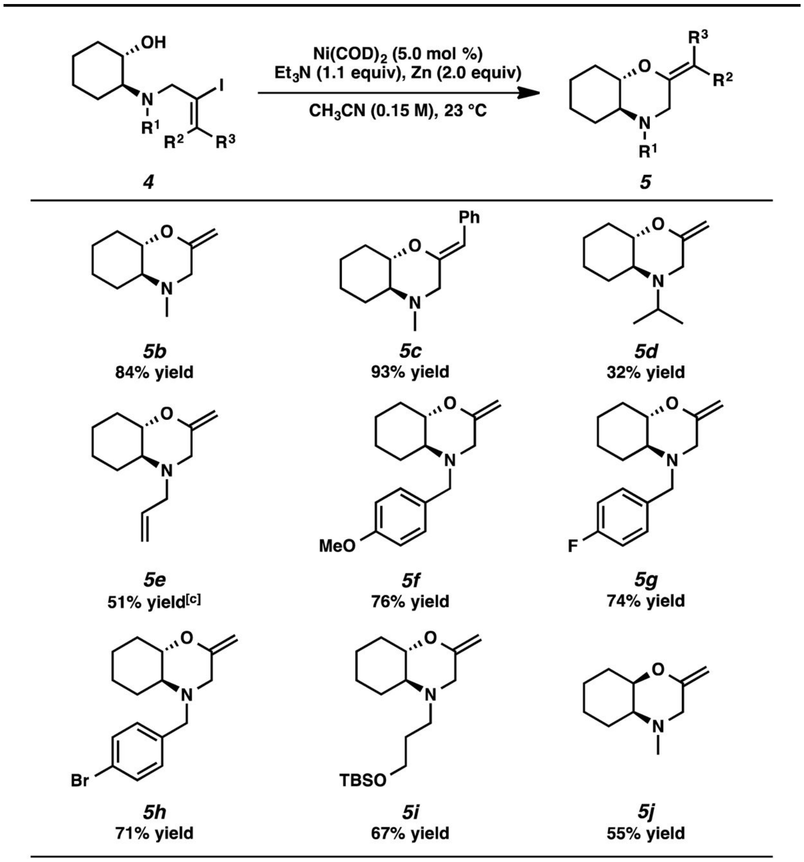
[b] Yield of isolated product.

[c] DMF (0.04 M) was used as a co-solvent.

[d] The reaction proceeded with incomplete conversion of starting material.

Table 2

Intramolecular Cross-Coupling of Amino-cyclohexanols[a],[b]



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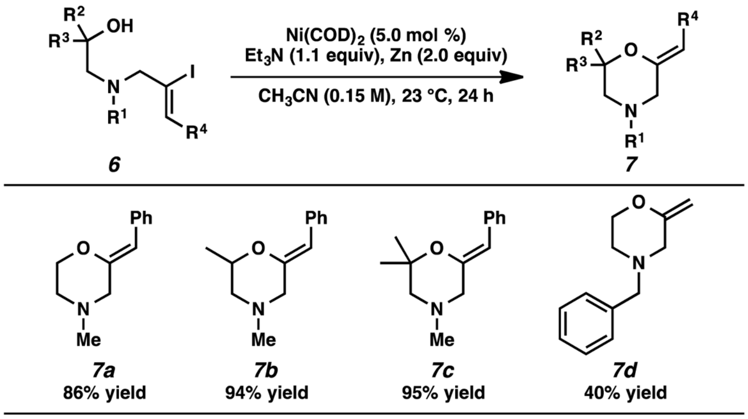
[a] Reactions were performed in a N_2-filled glove box.

[b] Yield of isolated product.

[c] 96 h.

Table 3

Intramolecular Cross-Coupling of Linear Aminoalcohols[a],[b]

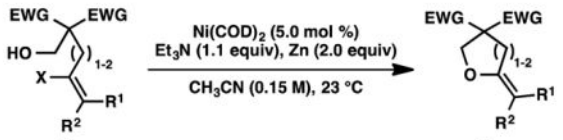


[a] Reactions were performed in a N_2-filled glove box.

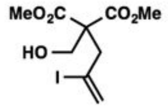
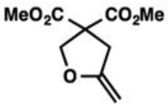
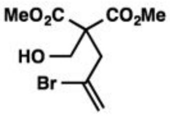
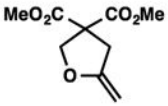
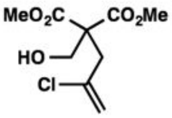
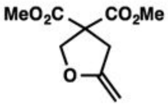
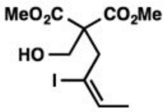
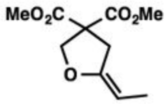
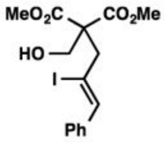
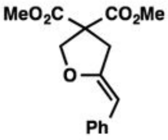
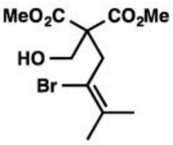
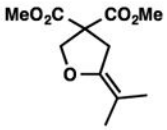
[b] Yield of isolated product.

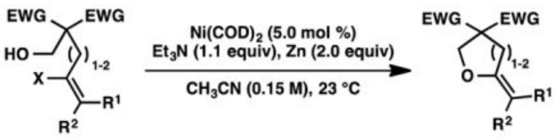
Table 4

Synthesis of Substituted Tetrahydrofuran and Dihydropyran Rings[a]

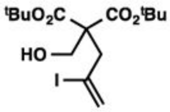
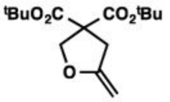
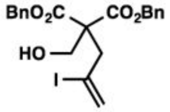
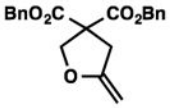
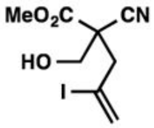
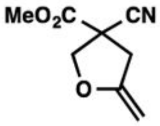
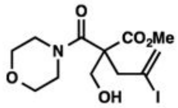
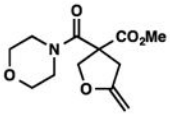
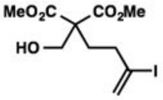
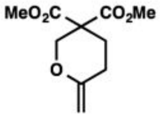
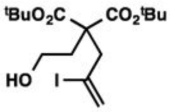
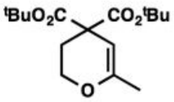


8 *9*

entry	substrate	product	time (h)	yield (%)[b]
1	 *8a*	 *9a*	1	87
2	 *8b*	 *9b*	12	52
3	 *8c*	 *9c*	60	–[c]
4	 *8d*	 *9d*	2	87
5	 *8e*	 *9e*	12	91
6	 *8f*	 *9f*	48	98



8 **9**

entry	substrate	product	time (h)	yield (%)[b]
7	 **8g**	 **9g**	1	87
8	 **8h**	 **9h**	1	66
9	 **8i**	 **9i**	12	61
10	 **8j**	 **9j**	1	70
11	 **8k**	 **9k**	72	_[c]
12	 **8l**	 **9l**	12	76

[a] Reactions were performed in a N_2-filled glove box.

[b] Yield of isolated product.

[c] Low conversion.