Cross-Coupling

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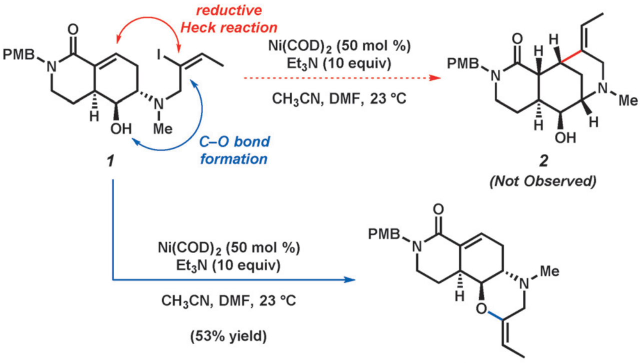
Nickel-Catalyzed Intramolecular C–O Bond Formation: Synthesis of Cyclic Enol Ethers

*Seo-Jung Han, Ryohei Doi, and Brian M. Stoltz**

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.*

Transition metal-catalyzed cross-coupling reactions have served as 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 nickel(II) alkoxide complexes is often cited as being significantly challenging, even at elevated temperatures.[4] To circumvent this challenge, stoichiometric oxidation of nickel(II) to the less stable nickel(III) analogues has been required. Additionally, reductive elimination of nickel(II) alkoxides is reported to be endothermic by computational analysis. This data is in contrast to that of palladium(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 either preformed sodium alkoxides or sodium siloxides.[6] In 2014, the group of Ranu 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 with respect to the nucleophiles is limited to either preformed 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 did not observe their desired C–O coupling products in the absence of either the photocatalyst or light. Although palladium- or copper-catalyzed C–O bond-forming reactions have been significantly developed, most of these reactions require high temperatures and thus 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.[9–11] To our knowledge, a mild and efficient nickel-catalyzed intramolecular cross-coupling cyclization between aliphatic hydroxy nucleophiles and tethered vinyl halides is unprecedented.

In the course of an alkaloid synthesis effort, we attempted a nickel-catalyzed reductive Heck reaction of the vinyl iodide **1** with the aim of producing the 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 hydroxy group furnished the 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.



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Scheme 1. Nickel-catalyzed C–O bond formation. cod = 1,5-cyclooctadiene, DMF = *N*,*N*-dimethylformamide, PMB = *para*-methoxybenzyl.

Given this interesting preliminary data, we chose the 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 a reduced catalyst loading (i.e., 20 mol % [Ni(COD)$_2$]; entry 6). Gratifyingly, the use of 2 equivalents of zinc powder as an additive resulted

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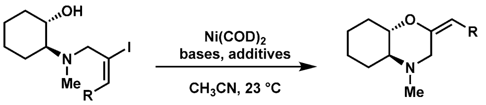
Table 1: Optimization of reaction parameters.[a]



R = Me (*4a*)
R = H (*4b*)

R = Me (*5a*)
R = H (*5b*)

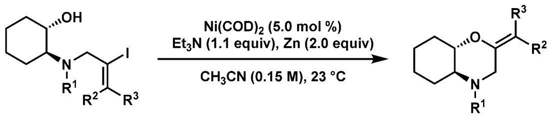
entry	sub-strate	conc. [M]	mol% Ni	base (equiv)	additive (equiv)	yield [%][b]
1[c]	**4a**	0.02	50	Et_3N (10)	–	53
2[c]	**4b**	0.02	50	Et_3N (10)	–	42
3[c]	**4a**	0.02	35	Et_3N (10)	–	42[d]
4[c]	**4a**	0.02	35	Cs_2CO_3 (3.0)	–	30[d]
5[c]	**4a**	0.02	35	K_3PO_4 (3.0)	–	34[d]
6	**4b**	0.10	20	Et_3N (1.0)	DABCO (1.0)	69
7	**4b**	0.10	20	Et_3N (1.0)	CsF (1.0)	51
8	**4a**	0.04	20	DABCO (1.0)	–	24
9	**4a**	0.04	20	DABCO (2.0)	–	50[d]
10	**4b**	0.15	5	Et_3N (1.1)	Zn (2.0)	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 the starting material. DABCO = 1,4-diazabicyclo[2.2.2]octane.

in a significant improvement in yield (84%) with only 5 mol% of [Ni(COD)$_2$] (entry 10).[13–17]

With optimized reaction 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 the vinyl ether **5c** in high yield and without loss of olefin stereochemical fidelity. Aminocyclohexanols bearing isopropyl and allyl substituents on the nitrogen atom 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–h**). Additionally, a silyl ether group remained intact, thus generating the substituted morpholine **5i** in good yield. Moreover, we discovered that a *cis*-aminocyclohexanol-derived substrate was competent in the reaction, thus providing the *cis*-fused bicyclic product **5j**.

Table 2: Intramolecular cross-coupling of amino-cyclohexanols.[a,b]



4

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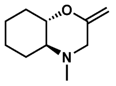
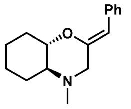
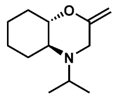


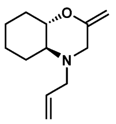
5b
84% yield



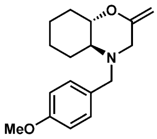
5c
93% yield



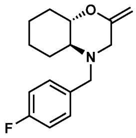
5d
32% yield



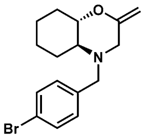
5e
51% yield[c]



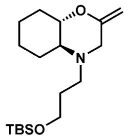
5f
76% yield



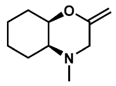
5g
74% yield



5h
71% yield



5i
67% yield

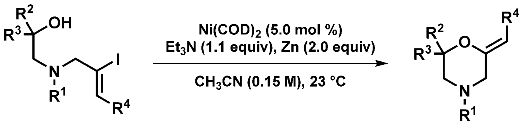


5j
55% yield

[a] Reactions were performed in a N_2-filled glove box. [b] Yield is that of isolated product. [c] 96 h. TBS = *tert*-butyldimethylsilyl.

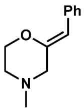
To our delight, we found that the nickel-catalyzed intramolecular etherification reactions also proceeded with linear aminoalcohol substrates to generate monocyclic morpholine derivatives in moderate to high yields (Table 3). The steric environment of the alcohol fragment did not hinder the performance,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

Table 3: Intramolecular cross-coupling of linear aminoalcohols.[a,b]

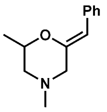


6

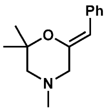
7



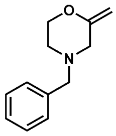
7a
86% yield



7b
94% yield



7c
95% yield

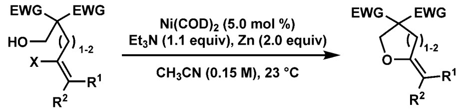


7d
40% yield

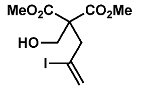
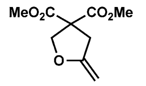
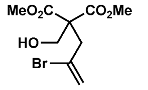
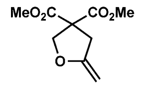
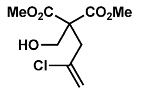
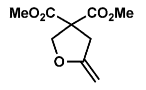
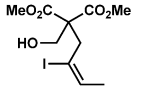
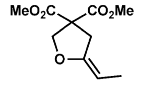
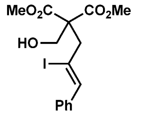
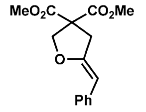
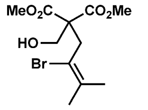
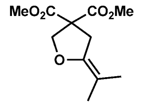
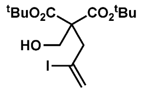
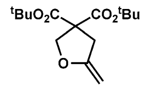
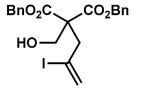
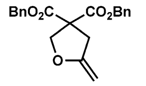
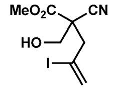
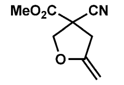
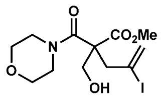
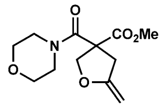
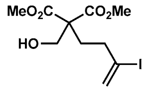
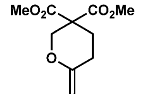
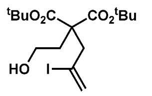
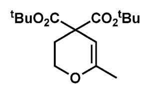
[a] Reactions were performed in a N_2-filled glove box. [b] Yield of isolated product.

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 the vinyl iodide **8a** furnished the cyclic ether **9a** in good yield after only 1 hour (entry 1). Although less reactive, a vinyl bromide (**8b**) also fared well in the reaction, thus affording the corresponding product in 52% yield after 12 hours (entry 2). Unfortunately, attempts to employ a vinyl chloride as the coupling partner led predominantly to recovery of the starting material (entry 3). Monomethyl- and monophenyl-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, the 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

Table 4: Synthesis of substituted tetrahydrofuran and dihydropyran rings.[a]



8 *9*

entry	substrate	product	*t* [h]	yield [%][b]
1	 *8a*	 *9a*	1	87
2	 *8b*	 *9a*	12	52
3	 *8c*	 *9a*	60	–[c]
4	 *8d*	 *9d*	2	87
5	 *8e*	 *9e*	12	91
6	 *8f*	 *9f*	48	98
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. EWG = electron-withdrawing group.

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 the 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 the 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, thus 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.

Acknowledgments

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[1] Selected recent reviews: a) F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270–5298; b) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417–1492; c) J. F. Hartwig, *Nature* **2008**, *455*, 314–322; d) J. Terao, N. Kambe, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663–672.

[2] a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299–309; b) V. P. Ananikov, *ACS Catal.* **2015**, *5*, 1964–1971.

[3] Selected recent reviews: a) M. R. Netherton, G. C. Fu, *Adv. Synth. Catal.* **2004**, *346*, 1525–1532; b) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; c) X. Hu, *Chem. Sci.* **2011**, *2*, 1867–1886; d) E. A. Standley, S. Z. Tasker, K. L. Jensen, T. F. Jamison, *Acc. Chem. Res.* **2015**, *48*, 1503–1514.

[4] For fundamental studies involving stoichiometric amounts nickel alkoxides, see: a) P. T. Matsunaga, G. L. Hillhouse, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 2075–2077; b) R. Han, G. L. Hillhouse, *J. Am. Chem. Soc.* **1997**, *119*, 8135–8136.

[5] S. A. Macgregor, G. W. Neave, C. Smith, *Faraday Discuss.* **2003**, *124*, 111–127.

[6] G. Mann, J. F. Hartwig, *J. Org. Chem.* **1997**, *62*, 5413–5418.

[7] D. Kundu, P. Maity, B. C. Ranu, *Org. Lett.* **2014**, *16*, 1040–1043.

[8] J. A. Terrett, J. D. Cuthbertson, V. W. Shurtleff, D. W. C. MacMillan, *Nature* **2015**, *524*, 330–334.

[9] For examples of intramolecular C–O cyclization using non-nickel catalysis, see: a) M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334; b) K. E. Torraca, S.-I. Kuwabe, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908; c) S.-i. Kuwabe, K. E. Torraca, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206; d) C. Sun, Y. Fang, S. Li, Y. Zhang, Q. Zhao, S. Zhu, C. Li, *Org. Lett.* **2009**, *11*, 4084–4087; e) Y. Fang, C. Li, *J. Am. Chem. Soc.* **2007**, *129*, 8092–8093; f) Y. Fang, C. Li, *Chem. Commun.* **2005**, 3574–3576.

[10] For examples of intermolecular C–O cyclization using non-nickel catalysis, see: a) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; b) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378; c) C. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 4321–4326; *Angew. Chem.* **2006**, *118*, 4427–4432; d) C. A. Parrish, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 2498–2500; e) Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719; f) X. Wu, B. P. Fors, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 9943–9947; *Angew. Chem.* **2011**, *123*, 10117–10121; g) R. Surasani, D. Kalita, A. V. D. Rao, K. B. Chandrasekhar, *Beilstein J. Org. Chem.* **2012**, *8*, 2004–2018; h) D. Maiti, S. L. Buchwald, *J. Org. Chem.* **2010**, *75*, 1791–1794; i) J. Niu, P. Guo, J. Kang, Z. Li, J. Xu, S. Hu, *J. Org. Chem.* **2009**, *74*, 5075–5078; j) G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979; k) R. E. Shade, A. M. Hyde, J.-C. Olsen, C. A. Merlic, *J. Am. Chem. Soc.* **2010**, *132*, 1202–1203.

[11] For an example of a base-mediated intramolecular synthesis of an alkylidene morpholine by C–O bond formation, see: A. T. Bottini, J. A. Mullikin, C. J. Morris, *J. Org. Chem.* **1964**, *29*, 373–379.

[12] M. Teng, W. Zi, D. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 1814–1817; *Angew. Chem.* **2014**, *126*, 1845–1848.

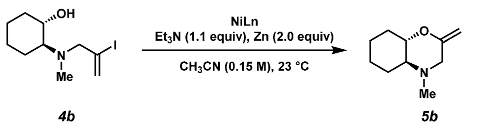
[13] S. A. Lebedev, V. S. Lopatina, E. S. Petrov, I. P. Beletskaya, *J. Organomet. Chem.* **1988**, *344*, 253–259.

[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 the vinyl iodide **4b** proceeded with 5 mol% of either NiI$_2$ or [NiBr$_2$(dme)] to furnish the vinyl ether **5b** (see entries 1 and 2 below). An increased rate of cycloetherification was observed with 10 mol% of [NiBr$_2$(dme)] (entries 2 and 3). Unfortunately, attempts to convert the vinyl iodide **4b** into the enol ether **5b** outside a N$_2$-filled glove box were unsuccessful (entries 4 and 5).

[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 either the aminocyclohexanol **4a** or **4b** proceeded, even without Zn powder, despite low yields and catalyst turnover (see Table 1), we envision that Zn powder likely plays an important role as a scavenger of the forming HI.



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

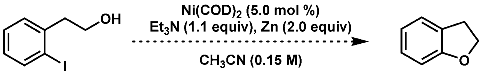
[18] M. Kurosu, M.-H. Lin, Y. Kishi, *J. Am. Chem. Soc.* **2004**, *126*, 12248–12249.

[19] W. R. Bowman, C. F. Bridge, P. Brookes, M. O. Cloonan, D. C. Leach, *J. Chem. Soc. Perkin Trans. 1* **2002**, 58–68.

[20] H. Cao, J. Yu, X. Z. Wearing, C. Zhang, X. Liu, J. Deschamps, J. M. Cook, *Tetrahedron Lett.* **2003**, *44*, 8013–8017.

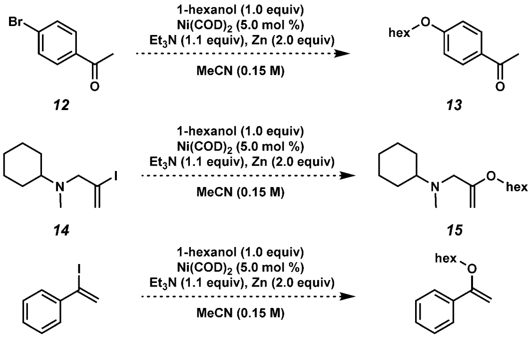
[21] M. Gatti, E. Drinkel, L. Wu, I. Pusterla, F. Gaggia, R. Dorta, *J. Am. Chem. Soc.* **2010**, *132*, 15179–15181.

[22] Although we attempted to construct the 2,3-dihydrobenzofuran **11** from the aryl iodide **10** under our standard reaction conditions, only unreacted starting material was recovered.



10 **11** **(Not Observed)**

[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.



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