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An in Situ Approach for Nickel-Catalyzed Cycloaddition

Thomas N. Tekavec, Gang Zuo, Kristina Simon, and
Janis Louie*

Department of Chemistry, University of Utah,
315 South 1400 East, Salt Lake City, Utah 84112

louie@chem.utah.edu

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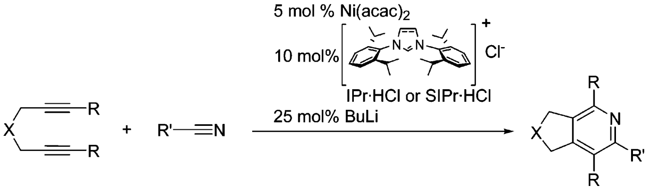
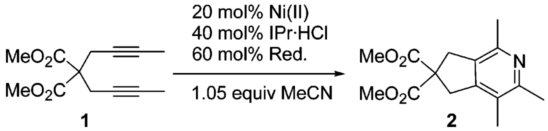


A convenient method for preparing pyridines from air-stable, commercially available catalyst precursors is described. The addition of *n*-BuLi to Ni(acac)$_2$ and an NHC salt (such as IPr•HCl or SIPr•HCl) rapidly generates an active Ni(0)/NHC catalyst for the cycloaddition of diynes and nitriles that affords pyridines without a decrease in observed yields. The in situ method also converts diynes and carbon dioxide to the corresponding pyrones.

Our group has been actively involved in developing methods for the preparation of a variety of heterocycles.[1] We discovered that the combination of Ni(COD)$_2$ and sterically hindered, electron-donating *N*-heterocyclic carbene ligands (NHC) catalyzes the cycloaddition reaction of unsaturated hydrocarbons with heterocumulenes and provides heterocycles such as pyrones,[2] pyridones,[3] pyrans,[4] and pyridines[5] under mild conditions. One drawback of this method is the use of air-sensitive compounds such as Ni(COD)$_2$ and the free NHC ligands. In an effort to expand the applicability and convenience of this chemistry, we have explored the use of air-stable, readily available precursors that produce the active Ni(0)/NHC catalyst in situ.

The standard reaction of a dimethyl 2,2-*di*-but-2-ynylmalonate (**1**) and acetonitrile was chosen as a model cycloaddition to evaluate reaction parameters (eq 1).[5] Our initial screen centered around finding a suitable combination of Ni(II) salt and reductant that would not only generate the Ni(0) but would also simultaneously deprotonate the imidazolium salt under reaction conditions.[6] Accordingly, we evaluated several Ni(II) salts in conjunction with reasonable reductants (Table 1). Both NiCl$_2$[6c] and NiCp$_2$[6e] have been used to provide Ni−NHC compounds in situ to catalyze coupling reactions. However, under our reaction conditions, pyridines were observed only when Ni(acac)$_2$ was used as a nickel source. Only *n*-BuLi served as both an effective base and reductant to provide a quantitative yield of the pyridine (entry 9). Moreover, catalyst formation and the reaction were performed at room temperature eliminating the need for a cryogen.

TABLE 1. Evaluation of Ni(II) Salts and Reductants in the Ni-Catalyzed Cycloadditions of Diyne 1 and Acetonitrile[a]



(1)

entry	Ni(II)	reductant	conversion[b] (%)	yield[b] (%)
1c	NiCl$_2$	Zn, Na$_2$CO$_3$	22	0
2	NiCl$_2$	*n*-BuLi	40	0
3	NiCl$_2$	DIBAL	29	0
4c	NiCp$_2$	Zn, Na$_2$CO$_3$	9	0
5	NiCp$_2$	*n*-BuLi	0	0
6	NiCp$_2$	DIBAL	0	0
7[c]	Ni(acac)$_2$	Zn, Na$_2$CO$_3$	27	0
8	**Ni(acac)$_2$**	***n*-BuLi**	**100**	**97**
9	Ni(acac)$_2$	DIBAL	0	0

[a] Reaction conditions: 0.1 M diyne **1**, 0.105 M MeCN, 20 mol % Ni(II), 40 mol % IPr•HCl, 60 mol % reductant, hexanes, room temperature. [b] Determined by GC. [c] 20 mol % Zn and 40 mol % Na$_2$CO$_3$ were used.

TABLE 2. Evaluation of NHC Salts[a]

entry	NHC salt	conversion[b] (%)	yield[b] (%)
1	IPr•HBF$_4$	100	80
2	IPr•HCl	100	80
3	SIPr•HCl	100	78
4	none	54	0

[a] Reaction conditions: 0.1 M diyne **1**, 0.105 M MeCN, 20 mol % Ni(acac)$_2$, 40 mol % NHC salt, 60 mol % reductant, hexanes, room temperature. [b] Determined by GC.

During our earlier investigations involving the cycloaddition of carbon dioxide, we found the active Ni(IPr)$_n$ catalyst could be generated by reacting Ni(COD)$_2$ with a solution of IPr•HBF$_4$ and KO-*t*-Bu. Interestingly, IPr•HCl was ineffective, and no pyrone product was observed.[2a] In contrast, when Ni(acac)$_2$ and *n*-BuLi are employed, both IPr salt precursors could be used without compromising heterocycle yields (entries 1 and 2, Table 2). No noticeable difference in yield was observed with the saturated NHC ligand, SIPr•HCl (entry 3).[7] In the absence of NHC salt, no product was observed as expected (entry 4). A

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(1) (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(2) (a) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Tekavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188. (b) Tekavec, T. N.; Arif, A. M.; Louie, J. *Tetrahedron* **2004**, *60*, 7431.

(3) (a) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (b) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098.

(4) Tekavec, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037.

(5) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030.

(6) (a) Böhm, V. P. W.; Gstöttmayr, C. W. K.; Westkamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387. (b) Gradel. B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 5689. (c) Sato, Y.; Sawaki, R.; Mori, M. *Organometallics* **2001**, *20*, 5510. (d) Desmartes, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029. (e) Kelly, R. A. III; Scott, M.; Díez-González, S.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 3442. (f) Inamoto, K.; Kuroda, J.; Danjo, T.; Sakamoto, T. *Synlett* **2005**, 1624.

(7) IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene.

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TABLE 3. Evaluation of Catalyst Loading and Reductant Concentration[a]

entry	$Ni(acac)_2$, mol %	IPr•HCl, mol %	*n*-BuLi, mol %	conversion[b] (%)	yield[b] (%)
1	20	40	60	100	81
2	10	20	30	100	90
3	5	10	15	65	57
4	2.5	5	7.5	27	21
5	1	2	3	0	0
6	5	10	20	94	89
7	5	10	25	100	91
8	5	10	30	100	90

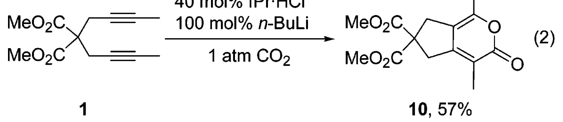
[a] Reaction conditions: 0.1 M diyne **1**, 0.105 M MeCN, hexanes, room temperature. [b] Determined by GC.

greater dependence on solvent was seen and may be due to the reactivity of the *n*-BuLi in various solvents. Cycloaddition proceeded smoothly in hexanes but was inhibited in other functionalized hydrocarbon solvents such as THF.

The next challenge was to lower $Ni(acac)_2$ loadings as typical cycloaddition reactions required only 5 mol % $Ni(COD)_2$. Thus, $Ni(acac)_2$ concentrations were systematically decreased while keeping the Ni:ligand ratios (1:2) and the Ni(II):*n*-BuLi ratios constant (1:3). Cycloadditions run with catalyst loadings of 10 mol % and higher gave quantitative diyne conversions (entries 1 and 2, Table 3). When 5 mol % was employed, a marked decrease in pyridine yield was observed (entry 3). We surmised that the reduction of the $Ni(acac)_2$ and deprotonation of the NHC salt by the stoichiometric amounts of *n*-BuLi may not be complete. It was possible that a small excess of *n*-BuLi was required to generate sufficient amounts of the Ni(0)/NHC catalyst. Indeed, 5 mol % $Ni(acac)_2$ adequately converted the diyne to pyridine when a small excess of *n*-BuLi (relative to $Ni(acac)_2$) was employed (entries 7 and 8). Importantly, pyridine yields did not depend on equilibration time of these catalyst precursors. Catalyst solutions of $Ni(acac)_2$, IPr•HCl, and *n*-BuLi prepared an hour in advance afforded the same yields as freshly prepared catalyst solutions.

A variety of pyridines[5] were prepared by using either of the readily available IPr•HCl or SIPr•HCl salts (Table 4). The in situ method converts both alkyl and aryl nitriles to their respective pyridines. Sterically hindered nitriles such as *o*-tolunitrile and *tert*-butylnitrile also reacted cleanly (entries 2 and 4, respectively). Diynes devoid of internal substitution, such as 3,9-dodecadiyne and diynes containing either an internal sulfonamide group or the analogous ether, also coupled with aryl nitriles to give the corresponding pyridines (entries 6−8). In all cases, air-stable, readily available catalyst precursors were employed and afforded pyridines in yields that were comparable to yields obtained with our previously reported $Ni(COD)_2$ and IPr system.[5]

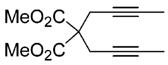
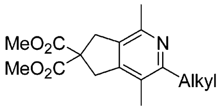
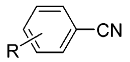
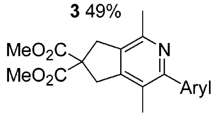
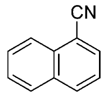
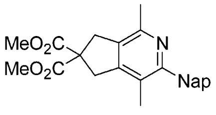
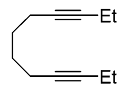
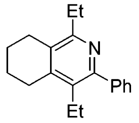
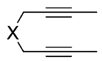
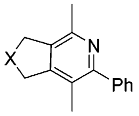
In an effort to expand this method, other heteroatom-containing substrates were explored as cycloaddition partners. As shown in eq 2, carbon dioxide and diyne **1** could be converted to the expected pyrone (**10**) in 57% yield although a higher catalyst loading was required.



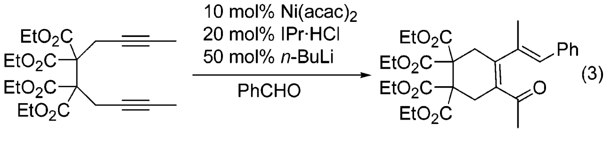
1 **10**, 57%

Reactions involving carbonyls (both aldehydes and ketones) and isocyanates were less successful. The reaction between diyne **11** and benzaldehyde did result in the formation of dienone **12**; however, low yields and multiple side products were obtained. The addition of a Lewis acid (e.g., $Ti(OiPr)_4$)[8] that could possibly enhance oxidative coupling had no effect on the transformation. Furthermore, reactions involving isocyanates afforded no desired pyridone heterocycles.

TABLE 4. In Situ Ni-Catalyzed Cycloaddition of Diynes and Nitriles

entry	diyne	nitrile	product, yield (%)[c]
			
1[a]	1	MeCN	**2** 64%
2[b]		*t*-BuCN	**3** 49%
			
3[a]	1	R = H	**4** 83%
4[b]	1	R = *o*-Me	**5** 80%
5[b]	1		 **6** 92%
			
6[a]		PhCN	**7** 84%
			
7[b]	X = NTs	PhCN	**8** 75%
8[a]	X = O	PhCN	**9** 85%

[a] Reaction conditions: 0.1 M diyne, 0.11 M nitrile, 5 mol % $Ni(acac)_2$, 10 mol % SIPr•HCl, 25 mol % *n*-BuLi, benzene, rt. [b] Reaction conditions: 0.1 M diyne, 0.105 M nitrile, 5 mol % $Ni(acac)_2$, 10 mol % IPr•HCl, 25 mol % *n*-BuLi, hexanes, rt. [c] Isolated yields (average of two runs).



11 **12**, trace

The combination of $Ni(acac)_2$, NHC salt, and *n*-BuLi generates an NHC-ligated Ni(0) catalyst in situ for the cycloaddition of diynes and nitriles. *n*-BuLi serves as both a base, which deprotonates the NHC salt, and a reductant, which converts the Ni(II) to the active Ni(0) catalyst. Pyridine yields were comparable to those obtained when using the standard $Ni(COD)_2$/NHC catalyst system. Thus, pyridines can be conveniently prepared at room temperature from inexpensive, air-stable, commercially available starting materials without requiring a drybox or special Schlenk equipment.

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[8] Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890 and references therein.

Experimental Section

Representative Procedure. To a stirring suspension of $Ni(acac)_2$ and (S)IPr•HCl in hexanes was added *n*-BuLi (2.5 M in hexanes) dropwise at room temperature. The resulting suspension was stirred for an additional 5 min at which time a solution of diyne (∼0.2 M in hexanes or toluene) was added followed by the nitrile. The reaction mixture was stirred at room temperature until no starting diyne was detected by TLC analysis (∼30 min). The reaction mixture was then quenched by the addition of 5 drops of MeOH and concentrated in vacuo. The residue was purified by flash column chromatography to yield the desired pyridine.

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Supporting Information Available: Experimental procedures and ^{1}H NMR, ^{13}C NMR, and IR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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