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Nickel-Catalyzed Cycloadditive Couplings of Enynes and Isocyanates

Brendan R. D'Souza and Janis Louie*

University of Utah, 315 S. 1400 E, Salt Lake City, Utah 84112

louie@chem.utah.edu

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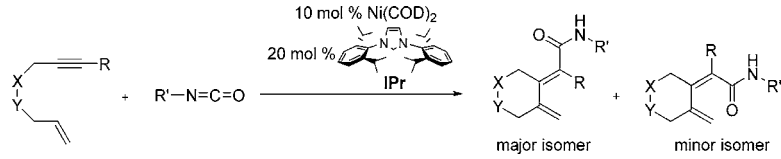
ABSTRACT



A mild and general route for preparing dienamides is described. Nickel imidazolylidene complexes were used to mediate cycloadditive coupling between enynes and isocyanates. Dienamides were prepared in excellent yields and with good *E*:*Z* selectivity. These dienamides can be further manipulated through oxidative cyclization methods. When a terminal enyne is employed, cyclization affords a lactam rather than a dienamide.

A primary interest of our group is the development of efficient cycloadditions that afford heterocycles and carbocycles.[1−7] We have found that Ni/NHC complexes effectively catalyze the cycloaddition of diynes with CO_2,[2] isocyanates,[3] carbonyls,[4] and nitriles.[5] These reactions afford pyrones, pyridones, pyrimidinones, pyrans, and pyridines in high yields. In addition, the same Ni/NHC system also mediates the rearrangement of vinyl cyclopropanes[6] and cyclopropylen-ynes.[7]

The efficacy of our Ni/NHC-catalyzed cycloaddition reactions that couple diynes/isocyanates[3] and enynes/carbonyls[4] prompted us to investigate the Ni/NHC-catalyzed cycloaddition of enynes and isocyanates. To date, only one catalytic system, which utilizes Rh catalysts, effectively cyclizes an olefin, an alkyne, and an isocyanate. This Rh catalyst was used to couple an alkenyl-isocyanate with an alkyne in the synthesis of Lasubine alkaloids.[8] Herein, we report our investigations involving the Ni-catalyzed reactions between enynes and isocyanates to afford dienamides.

Despite the precedent that enynes and isocyanates were both viable substrates *individually* in the Ni-catalyzed cycloaddition reaction, it was unclear whether they would react with each other in a productive manner. However, success in Ni-catalyzed reductive couplings between alkenes and alkyl-substituted isocyanates[9] suggested enynes and isocyanates would be reactive under Ni-catalyzed cycloaddition reaction conditions.

Our initial efforts revolved around evaluating a variety of conditions that would yield an isolable product. As shown in Table 1, a variety of phosphines and NHCs[10] were evaluated as prospective ligands to determine the potential reactivity between enyne (**1a**) and cyclohexyl isocyanate (**2a**, eq 1). Attention was directed toward minimizing alkyne cyclotrimerization, a known side

(1) (a) Zhang, K.; Chopade, P. R.; Louie, J. *Tetrahedron Lett.* **2008**, *49*, 4306. (b) Zuo, G.; Zhang, K.; Louie, J. *Tetrahedron Lett.* **2008**, *49*, 6797.

(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. (c) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, *62*, 7552.

(4) (a) Tekavec, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037. (b) Tekavec, T. N.; Louie, J. *J. Org. Chem.* **2008**, *73*, 2641.

(5) (a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030. (b) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834.

(6) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2777.

(7) Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5798.

(8) (a) Yu, T. R.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782. (b) Yu, T. R.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (c) Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231.

(9) Scleicher, K. D.; Jamison, T. F. *Org. Lett.* **2007**, *9*, 875.

(10) IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene. SIPr = 1,3-bis(2,5-diisopropylphenyl)-4,5-dihydroimidazolin-2-ylidene. IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene. I^{t}Bu = 1,3-di-*tert*-butylimidazol-2-ylidene.

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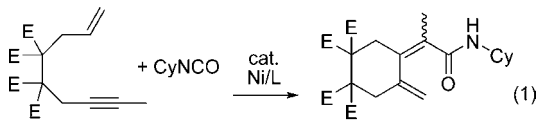
Table 1. Ni-Catalyzed Cycloaddition of Enyne **1** and CyNCO (**2a**)[a]



entry	L	% conversion of **1**[b]	% yield of **3**[b]
1	none	10	nd
2	P(*n*-Bu)$_3$	31	nd[c]
3	PPh$_3$	17	nd
4	P(*p*-Tol)$_3$	31	nd
5	DPPF	7	nd
6	BINAP	5	nd
7	biphenP(*t*-Bu)$_2$	17	nd
8	I*t*Bu	14	nd
9	IMes	33	nd
10	SIPr	90	78
11	IPr	100	80

[a] Reaction conditions: 10 mol % Ni(COD)$_2$, 20 mol % L, 0.1 M **1a**, 0.11 M **2a**, toluene, room temperature, 17 h. [b] Determined by GC using naphthalene as an internal standard. [c] nd = not detectable by GC.

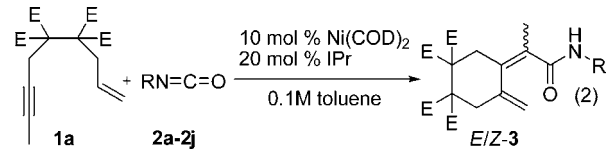
reaction.[11] In general, poor conversions of enyne **1a** were observed when either monodentate or bidentate phosphines were employed (entries 2−7). A slight increase in the conversion was observed when the reaction was run with bulky NHCs such as I^{t}Bu and IMes (entries 8 and 9). However, in all cases (entries 2−9), no detectable coupling product was observed. In contrast, when bulkier NHC ligands such as SIPr and IPr were employed, a distinct coupling product was isolated in good yields (entries 10 and 11). As expected, negligible coupling was observed when Ni(COD)$_2$ was used in the absence of an additional donor ligand (entry 1).

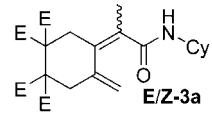
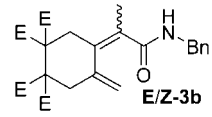
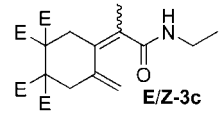
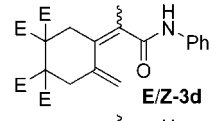
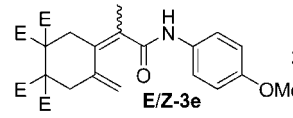
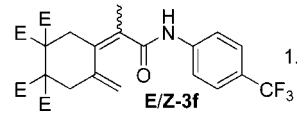
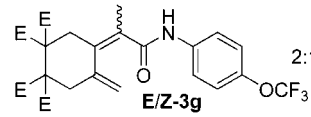
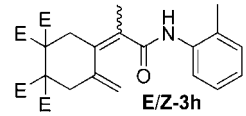
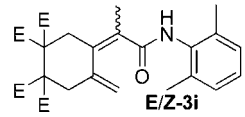
Isolation of the major product revealed that cyclization did indeed occur. Dienamide **3a**, rather than a lactam product that would arise from an additional carbon−nitrogen bond-forming event (vide infra), was isolated in 70% yield.

The combination of Ni and IPr catalyzed the coupling of enyne **1a** with a variety of isocyanates (Table 2, eq 2). Alkyl isocyanates reacted smoothly at room temperature within 1−2 h. Furthermore, these reactions afforded dienamides in excellent overall yields with good *E*:*Z* ratios (entries 1−3). In contrast, aryl isocyanates reacted more sluggishly and required slightly more forcing conditions.[9] For example, the Ni-catalyzed coupling of enyne **1a** and phenyl isocyanate proceeded at 60 °C while no reaction occurred at room temperature (entry 4). Nevertheless, dienamide **3d** was isolated in 89% yield. Aryl isocyanates possessing both electron-donating groups as well as electron-withdrawing groups were converted to their respective dienamides in 71−80% yield. Aryl isocyanates possessing electron-donating groups reacted faster than

(11) (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (b) Tsuda, T.; Morikawa, S.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140.

Table 2. Dienamide Formation from Enyne **1** and Isocyanates **2a**−**2j**[c]



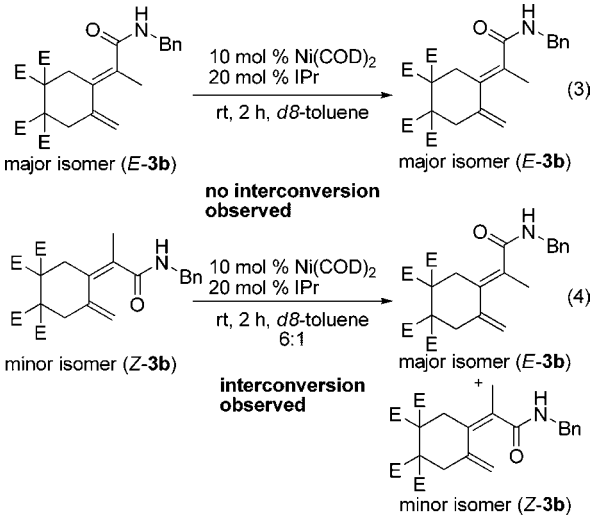
entry	*E*/*Z* products	*E*:*Z* ratio[a]	rxn temp	% yield[b]
1	 **E/Z-3a**	5:1	rt, 1 h	70
2	 **E/Z-3b**	2:1	rt, 2 h	68
3	 **E/Z-3c**	2:1	80 °C, 1 h	75
4	 **E/Z-3d**	2:1	60 °C, 2 h	79
5	 **E/Z-3e**	2:1	60 °C, 2 h	74
6	 **E/Z-3f**	1.8:1	100 °C, 7 h	57
7	 **E/Z-3g**	2:1	80 °C, 5 h	66
8	 **E/Z-3h**	2:1	80 °C, 1 h	71
9	 **E/Z-3i**	2:1	80 °C, 1.5 h	80

[a] Determined by ^{1}H NMR. [b] Isolated yields, average of 2 runs. [c] Reaction conditions: 1 equiv of **1a** 1 equiv of **2**.

those possessing electron-withdrawing groups (entries 5−7). Sterically hindered aryl isocyanates such as **2h** and **2i** were also converted to their respective dienamides, although under higher reaction temperatures, in excellent yields of 71% and 80%, respectively (entries 8 and 9). No reaction was observed when TMS-NCO was employed.

When either *E* or *Z* isomers of dienamide **3b** were resubjected to the nucleophilic IPr ligand, no isomerization was observed. In addition, when the *E*-isomer of **3b** was resubjected to the reaction conditions, no isomerization to the *Z*-dienamide was observed. However, when the *Z*-isomer

of **3b** was resubjected to the reaction conditions, a mixture of *E*- and *Z*-products was obtained (eq 4). Thus, the *Z*-dienamides are most likely the initial coupling product and undergo a Ni(0)-mediated interconversion to the more stable *E*-isomer over the course of the reaction.



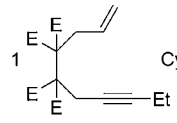
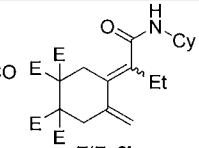
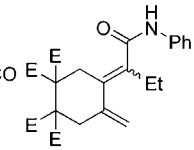
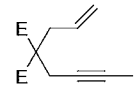
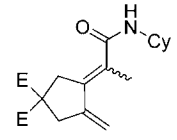
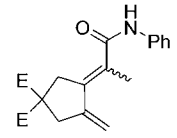
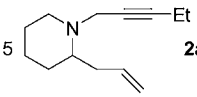
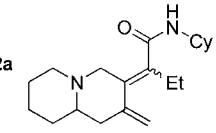
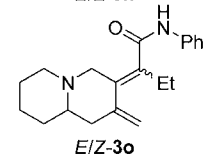
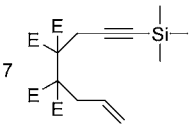
A variety of enynes were also successfully converted to their respective dienamide products (Table 3). A significant increase in dienamide yield (**3j** and **3k**) was observed when enyne **1b** was used as a coupling partner in lieu of enyne **1a** despite the similarity in the backbones of these two substrates (Table 3, entries 1 and 2 versus Table 2, entries 1 and 4, respectively). Enyne **1c** afforded a five-membered cyclic dienamide in good yield (entries 3 and 4). Dienamides having a bicyclic ring system with a nitrogen atom on the bridgehead were also prepared in good yields (entries 5 and 6). Somewhat surprisingly, although enyne **1e**, which possesses a bulky trimethylsilyl group on the alkyne, has been used as a substrate in other Ni-catalyzed cycloddition reactions,[2b] this enyne undergoes cycloisomerization[12] exclusively and does not afford a dienamide product (entries 7).

Two possible mechanisms for dienamide formation are depicted in Scheme 1.[13] In pathway A, intramolecular initial oxidiative coupling of the enyne and subsequent insertion of the isocyanate leads to seven-membered intermediate **5**. Rather than undergoing C−N bond-forming reductive elimination,[14] β-hydride elimination occurs resulting in **6**. Facile reductive elimination from **6** would afford the *Z*-dienamide product. Alternatively, nickelacycle **5** can arise from oxidative coupling of the alkyne and the isocyanate to produce **7** prior to insertion of the pendant olefin (pathway B, Scheme 1).[12]

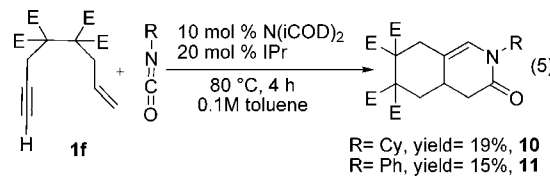
Interestingly, when enyne **1f** was subjected to the coupling conditions with either isocyanate **2a** or **2b**, dienamide formation did not occur. Instead, a cyclic amide was formed as the sole product, albeit in low yields (eq 5)

(12) Tekavac, T.; Louie, J. *Tetrahedron* **2008**, *64*, 6870.
(13) For an insightful discussion on the mechanism of the Rh catalyzed couplings of alkenes, alkynes, and isocyanates, see ref 8.

Table 3. Substrate Scope Using Enynes **1b**−**1e** and Isocyanates **2a** and **2b**[g]

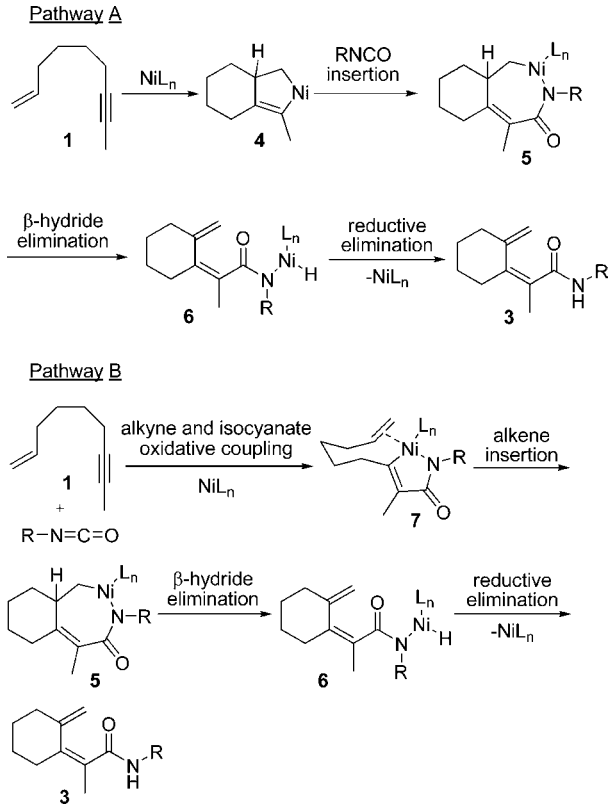
entry	enyne	isocyanate	*E*, *Z* products	*E*:*Z* ratio[a]	% yield[b]
1	 **1b**	CyNCO **2a**	 *E*/*Z*- **3j**	4:1	89[c]
2	**1b**	PhNCO **2b**	 *E*/*Z*-**3k**	4:1	84[d]
3	 **1c**	**2a**	 *E*/*Z*-**3l**	4:1	65[e]
4	**1c**	**2b**	 *E*/*Z*-**3m**	4:1	72[f]
5	 **1d**	**2a**	 *E*/*Z*-**3n**	1.4:1	72[f]
6	**1d**	**2b**	 *E*/*Z*-**3o**	1.4:1	72[f]
7	 **1e**	**2a**/**2b**	nd	—	—

[a] Determined by ^{1}H NMR. [b] Isolated yields, average of 2 runs. [c] rt, 4 h. [d] rt, 6 h. [e] 80 °C, 4 h. [f] 80 °C, 3 h. [g] Reaction conditions: 1 equiv of enyne, 1 equiv of isocyanate, 0.1 M toluene.

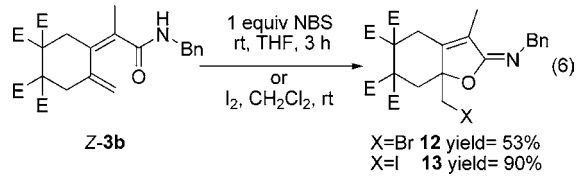


Lactams **10** and **11** likely arise from C−N bond-forming reductive elimination from a seven-membered nickelacycle such as **5b** (Scheme 2). Insertion of the isocyanate into the Ni−C_{sp3} bond, rather than the Ni−C_{sp2} bond in **4**, would lead to the formation of **5b** (mechanism A, Scheme 1). Alternatively, nickelacycle **5b** may arise from initial oxidative coupling between the olefin of the enyne and the isocyanate followed by

Scheme 1. Possible Mechanisms for Dienamide Formation

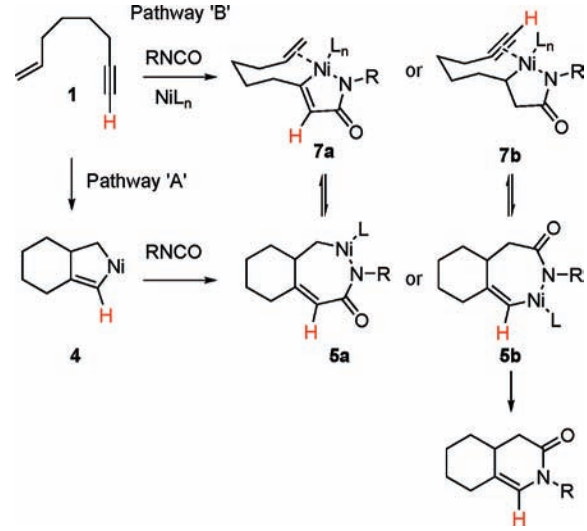


insertion of the pendant alkyne (mechanism B, Scheme 1). Formation of **5b** may be favored over **5a** when the steric interaction of the alkyne substituent and the ligand (i.e., IPr) is small. In fact, we have observed this type of sterically driven selectivity in other Ni-catalyzed cycloaddition chemistry.[2b,4]



Dienamides can be conveniently converted to iminoethers.[15] For example, the reaction of **3b** with NBS afforded

Scheme 2. Possible Mechanism for Lactam Formation



the bromo-substituted iminoether **12** in 53% isolated yield. Furthermore, when **3b** was subjected to I_2 in lieu of NBS, higher yields were obtained of the halo-substituted iminoether; that is, the iodo-substituted iminoether **13** was obtained in 90% isolated yield.

We have demonstrated that reductive coupling of enynes and isocyanates can successfully take place using $Ni(COD)_2$ and IPr ligand system to afford dienamides in good to excellent yields. This catalyst system can be used to prepare dienamides that contain five- or six-membered rings.

Acknowledgment. We gratefully acknowledge the Camille and Henry Drefus Foundation and the NIGMS for support of this research.

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

OL901703T

(14) Koo, K.; Hillhouse, G. *Organometallics* **1995**, *14*, 4421.
(15) Wang, C.; Lu, J.; Mao, G.; Xi, Z. *J. Org. Chem.* **2005**, *70*, 5150.