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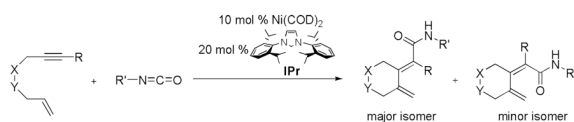
## Nickel Catalyzed Cycloadditive Couplings of Enynes and Isocyanates

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### Abstract



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

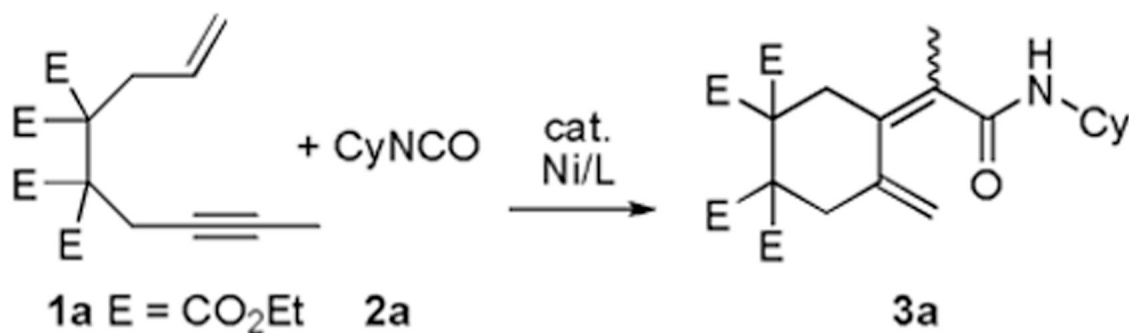
A primary interest of our group is the development of efficient cycloadditions that afford heterocycles and carbocycles.<sup>1–7</sup> We have found that Ni/NHC complexes effectively catalyze the cycloaddition of diynes with CO<sub>2</sub>,<sup>2</sup> isocyanates,<sup>3</sup> carbonyls,<sup>4</sup> and nitriles.<sup>5</sup> 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<sup>6</sup> and cyclopropylenynes.<sup>7</sup>

The efficacy of our Ni/NHC catalyzed cycloaddition reactions that couple diynes/isocyanates<sup>3</sup> and enynes/carbonyls<sup>4</sup> 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.<sup>8</sup> Herein, we report our investigations involving the Ni catalyzed reactions between enynes and isocyanates to afford dieneamides.

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<sup>9</sup> suggested enynes and isocyanates would be reactive under Ni catalyzed cycloaddition reaction conditions.

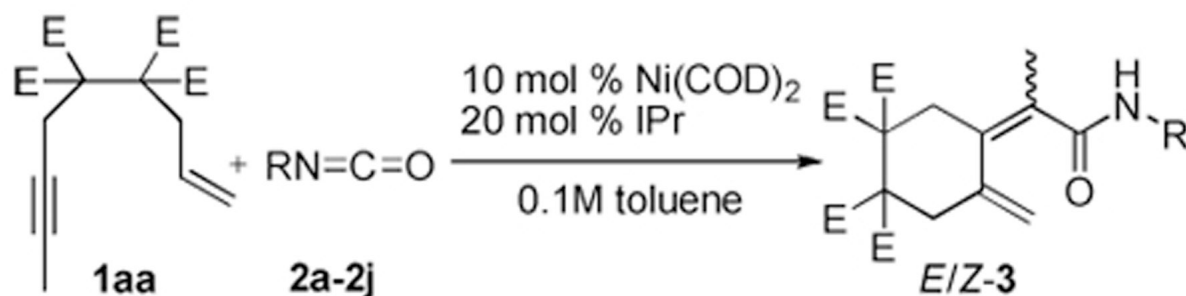
Our initial efforts revolved around evaluating a variety of conditions that would yield an isolable product. As shown in Table 1, a variety of phosphines and NHCs<sup>10</sup> were evaluated as prospective ligands to determine the potential reactivity between enyne (**1a**) and cyclohexyl isocyanate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

cyclotrimerization, a known side-reaction.<sup>11</sup> 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 *t*Bu and IMes (entries 8–9). 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 10–11). As expected, negligible coupling was observed when Ni(COD)<sub>2</sub> was used in the absence of an additional donor ligand (entry 1).



(1)

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

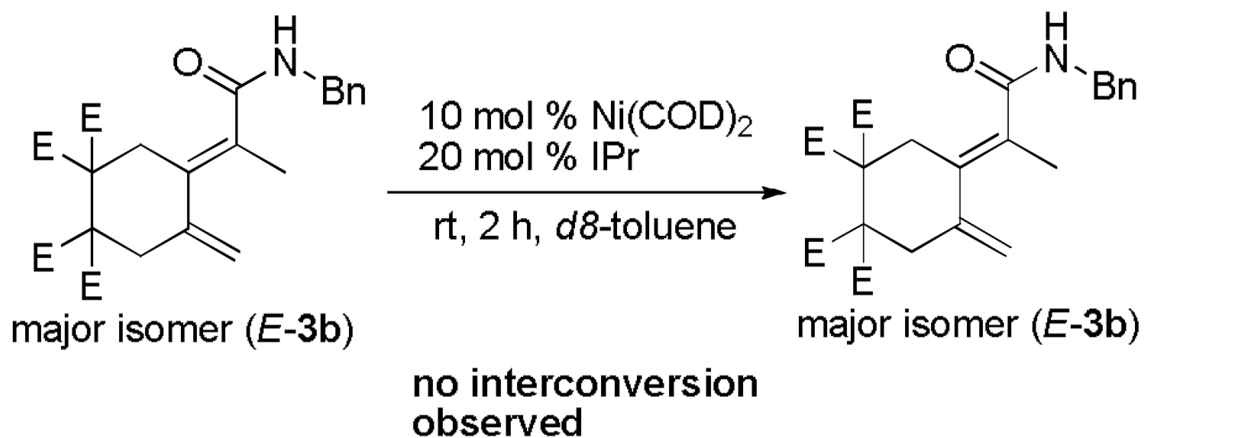


(2)

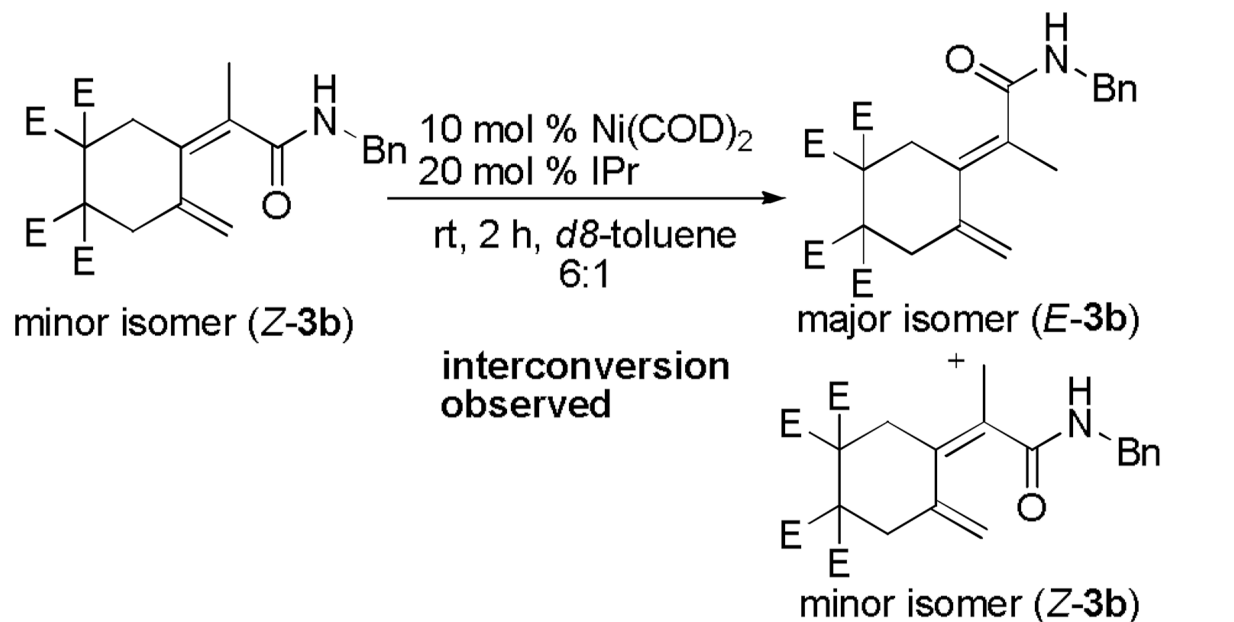
The combination of Ni and IPr catalyzed the coupling of enyne **1a** with a variety of isocyanates (Table 2, Equation 2). Alkyl isocyanates reacted smoothly at room temperature within 1–2 hours. Furthermore, these reactions afforded dieneamides in excellent overall yields with good *E:Z* ratios (entries 1–3). In contrast, aryl isocyanates reacted more sluggishly and required slightly more forcing conditions.<sup>9</sup> 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, dieneamide **3d** was isolated in 89% yield. Both aryl isocyanates possessing 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 those possessing electron-withdrawing groups (entries 5–7). Sterically-hindered aryl isocyanates such as **2h** and **2g** were also converted to their respective

dieneamides, although under higher reaction temperatures, in excellent yields, 91% and 92%, respectively (entries 8–9). No reaction was observed when TMS-NCO **2i** was employed.

When either *E* or *Z* isomers of dieneamide **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*-dieneamide was observed. However, when the *Z*-isomer of **3b** was resubjected to the reaction conditions, a mixture of *E*- and *Z*- products was obtained (Equation 4). Thus, the *Z*-dieneamides 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.



(3)



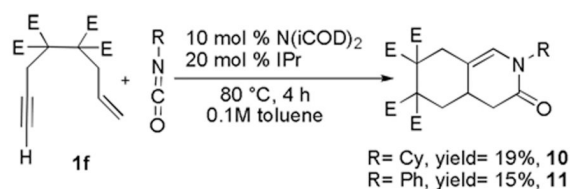
(4)

A variety of enynes were also successfully converted to their respective enamide products (Table 3). A significant increase in enamide 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 1–2 versus Table 2, entries 1 and 4, respectively). Enyne **1c** afforded a 5-membered cyclic dieneamide in good yield (entries 3–4).

Dienamides having a bicyclic ring system with a nitrogen atom on the bridgehead were also prepared in good yields (entries 5–6). Somewhat surprisingly, although enyne **1e**, which possesses a bulky trimethylsilyl group on the alkyne, has been used as a substrate in other Ni-catalyzed cycloaddition reactions,<sup>2b</sup> this enyne undergoes cycloisomerization<sup>12</sup> exclusively and does not afford a dienamide product (entries 7).

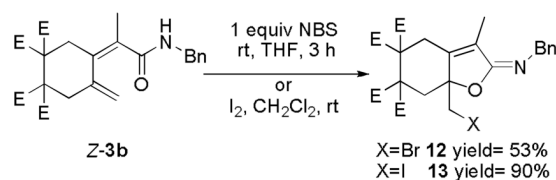
Two possible mechanisms for dienamide formation are depicted in Scheme 1.<sup>13</sup> The primary difference between these two mechanisms is at which point  $\beta$ -hydride elimination occurs. In pathway A, intramolecular initial oxidative coupling of the enyne and subsequent insertion of the isocyanate leads to 7-membered intermediate **5**. Rather than undergoing C–N bond-forming reductive elimination,<sup>14</sup>  $\beta$ -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).<sup>12</sup>

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 (Equation 5)



(5)

Lactams **10** and **11** likely arise from C–N bond-forming reductive elimination from a 7 membered nickelacycle such as **5b** (Scheme 2). Insertion of the isocyanate into the Ni–C<sub>sp3</sub> bond, rather than the Ni–C<sub>sp2</sub> 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 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.<sup>2b,4</sup>



(6)

Dienamides can be conveniently converted to iminoethers.<sup>15</sup> For example, the reaction of **3b** with NBS afforded the bromo-substituted iminoether **12** in 53% isolated yield. Furthermore, when **3b** was subjected to I<sub>2</sub> 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)<sub>2</sub> and IPr ligand system to afford dienamides in good to excellent yields.. This catalyst system can be used to prepare dienamides which contain 5 or 6-membered rings.

## Supplementary Material

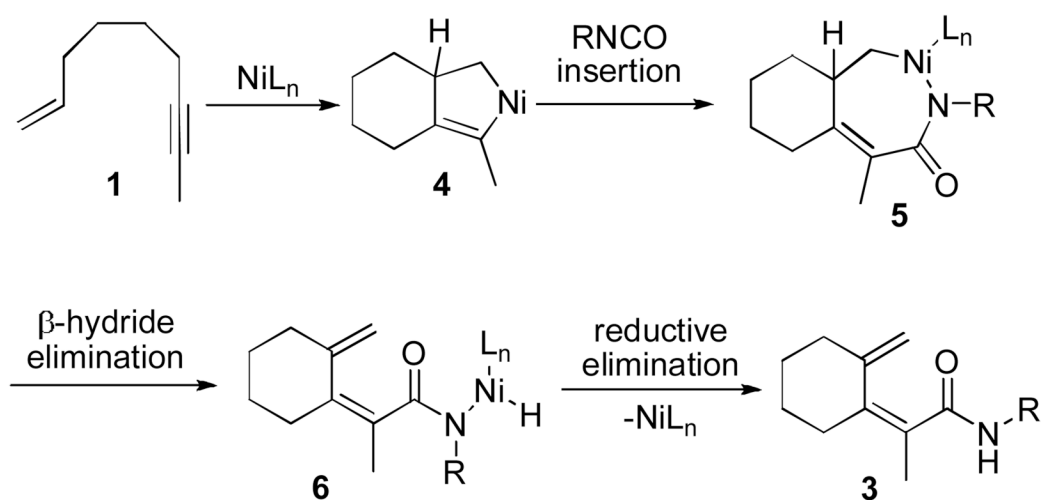
Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

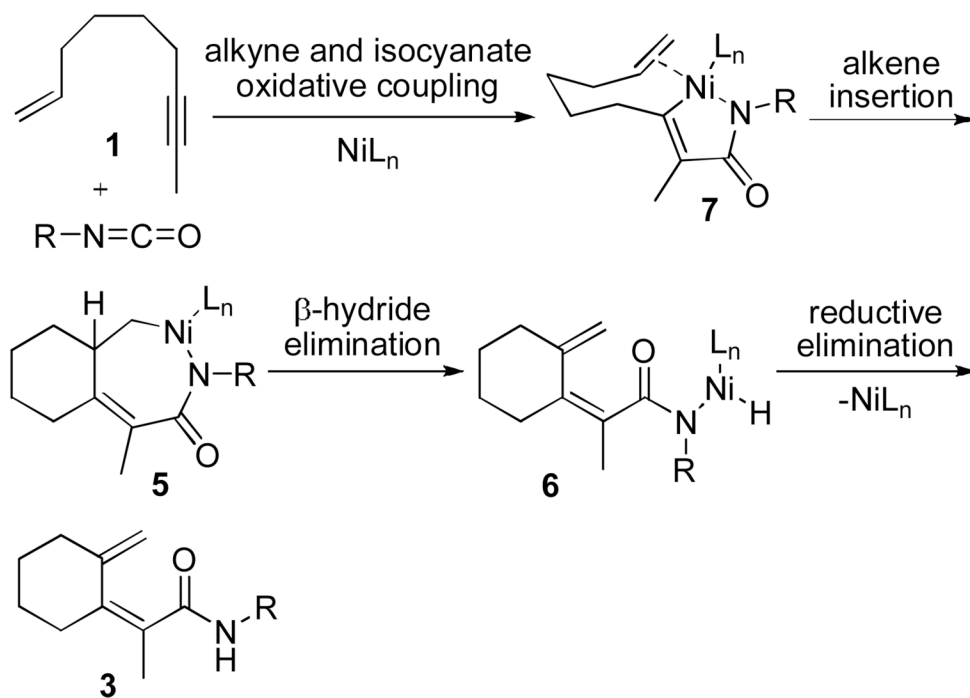
We gratefully acknowledge the Camille and Henry Dreyfus Foundation and the NIGMS for support of this research.

## References

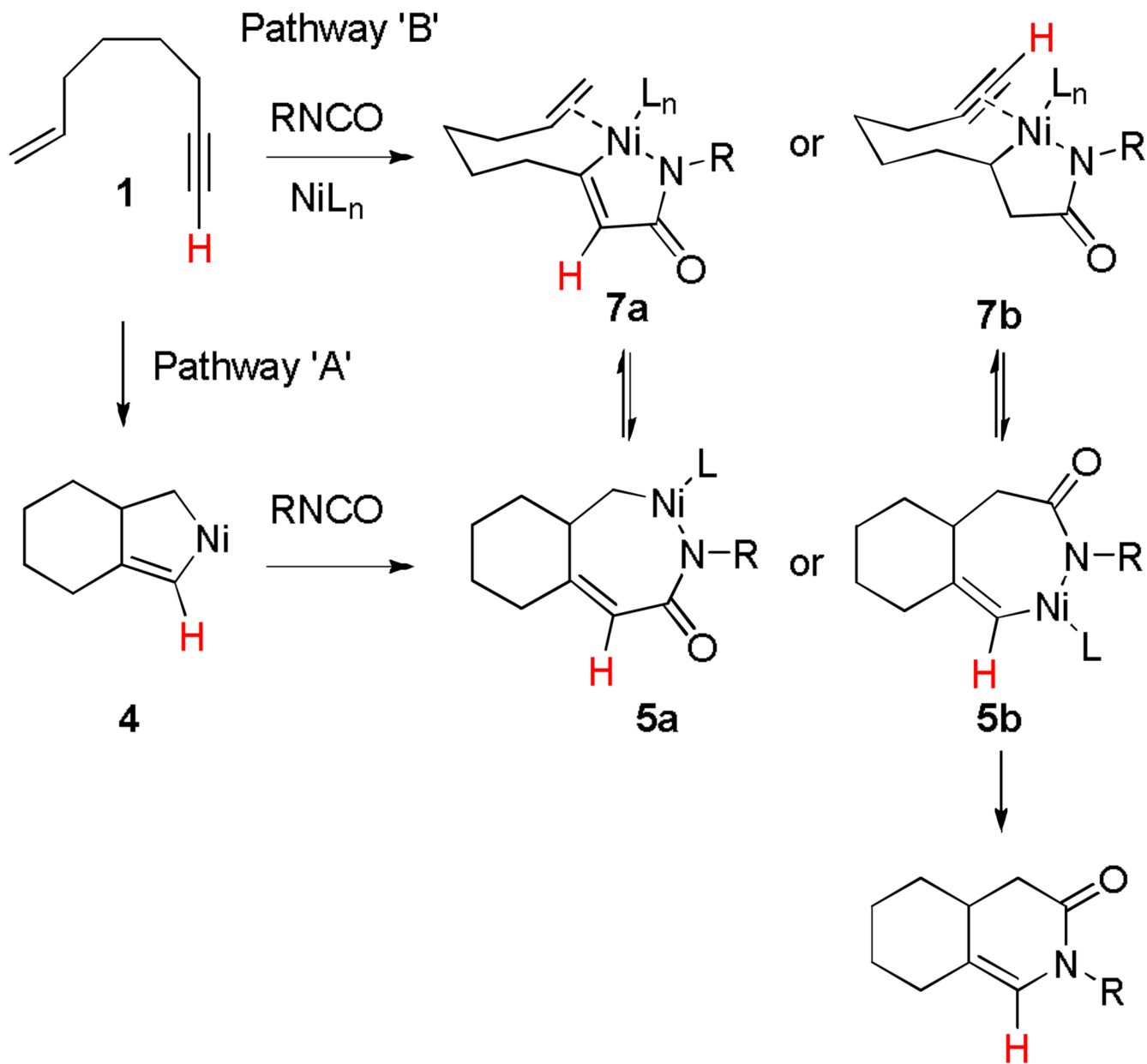
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### Pathway B



**Scheme 1.**  
Possible mechanisms for dieneamide formation



**Scheme 2.**  
Possible mechanisms for dienamide formation

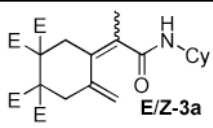
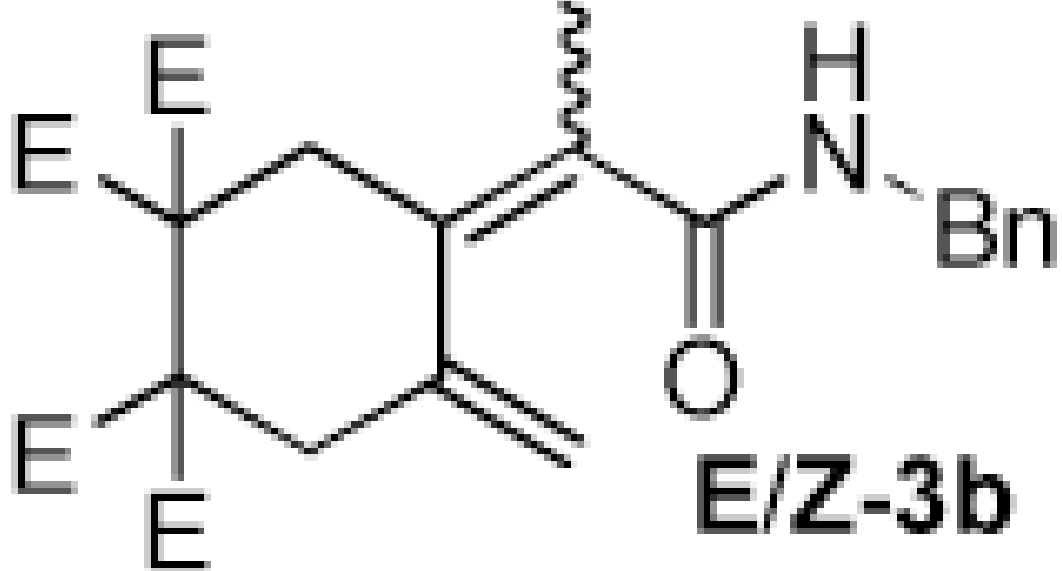
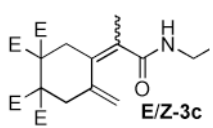
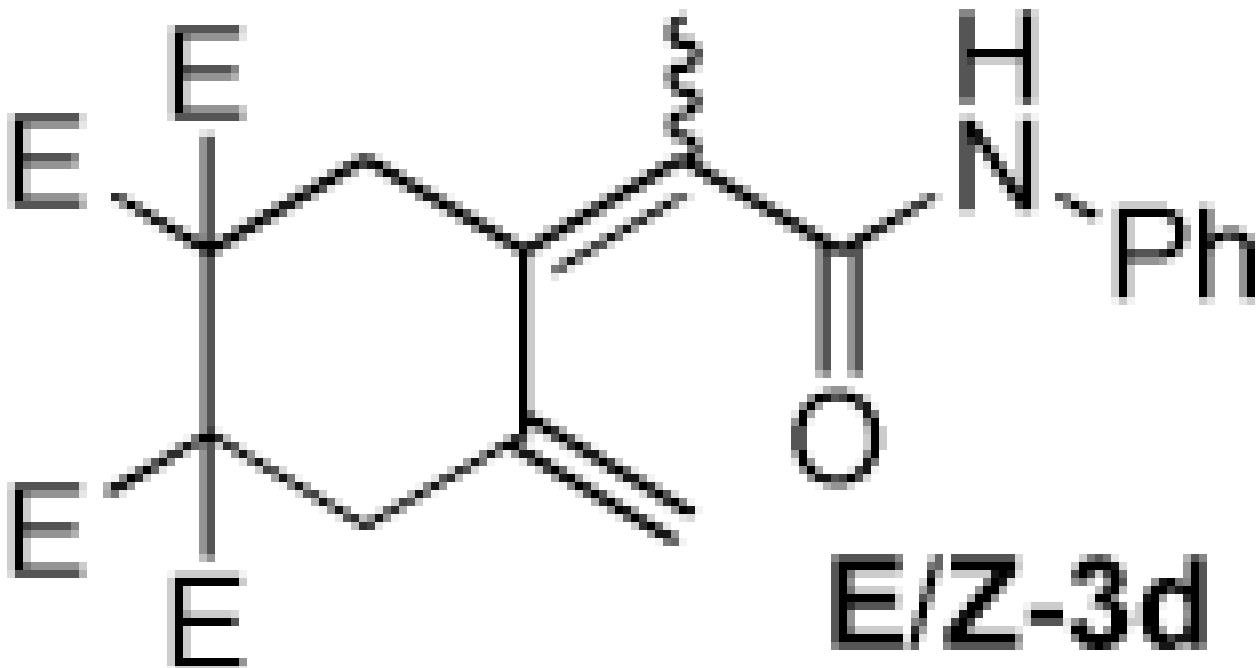
**Table 1**Ni-catalyzed cycloaddition of enyne **1** and CyNCO (**2a**)<sup>a</sup>

entry	L	% conversion of <b>1</b> <sup>b</sup>	% yield of <b>3</b> <sup>b</sup>
1	none	10	nd
2	P( <i>n</i> -Bu) <sub>3</sub>	31	nd <sup>c</sup>
3	PPh <sub>3</sub>	17	nd
4	P( <i>p</i> -Tol) <sub>3</sub>	31	nd
5	DPPF	7	nd
6	BINAP	5	nd
7	biphenP( <i>t</i> -Bu) <sub>2</sub>	17	nd
8	<i>It</i> Bu	14	nd
9	IMes	33	nd
10	SIPr	90	78
11	IPr	100	80

<sup>a</sup>Reaction conditions: 5 mol % Ni(COD)<sub>2</sub>, 10 mol % L, 0.1 M **1a**, 0.11 M **2a**, toluene, room temperature, 17 h.<sup>b</sup>Determined by GC using naphthalene as an internal standard.<sup>c</sup>nd = not detectable by GC.

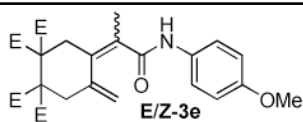


**Table 2**Dienamide formation from enyne **1** and isocyanates **2a-2j**

entry	<i>E/Z</i> products	<i>E/Z</i> ratio <sup>a</sup> rxn te
1	 <b>E/Z-3a</b>	5:1 rt, 1
2	 <b>E/Z-3b</b>	2:1 rt, 2
3	 <b>E/Z-3c</b>	2:1 80 °C
4	 <b>E/Z-3d</b>	2:1 60 °C

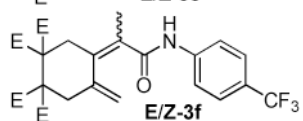
entry	<i>E/Z</i> products	<i>E/Z</i> ratio <sup>a</sup> rxn te
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5

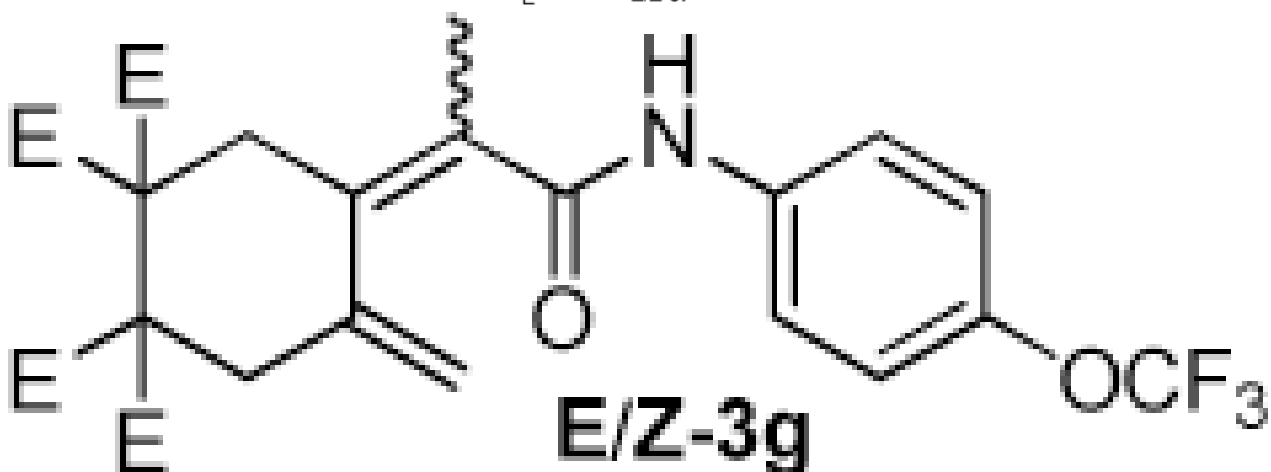


2:1 60 °C

6

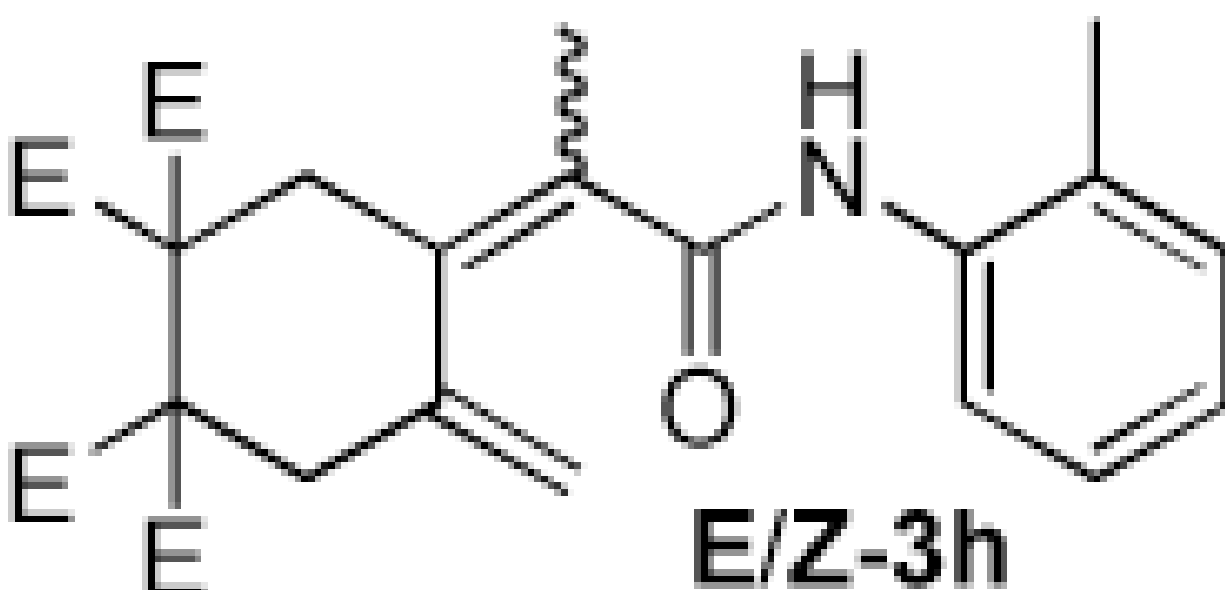
1.8:1 100 °C  
h

7



2:1 80 °C

8



2:1 80 °C

9

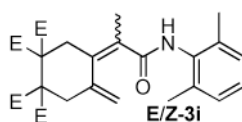
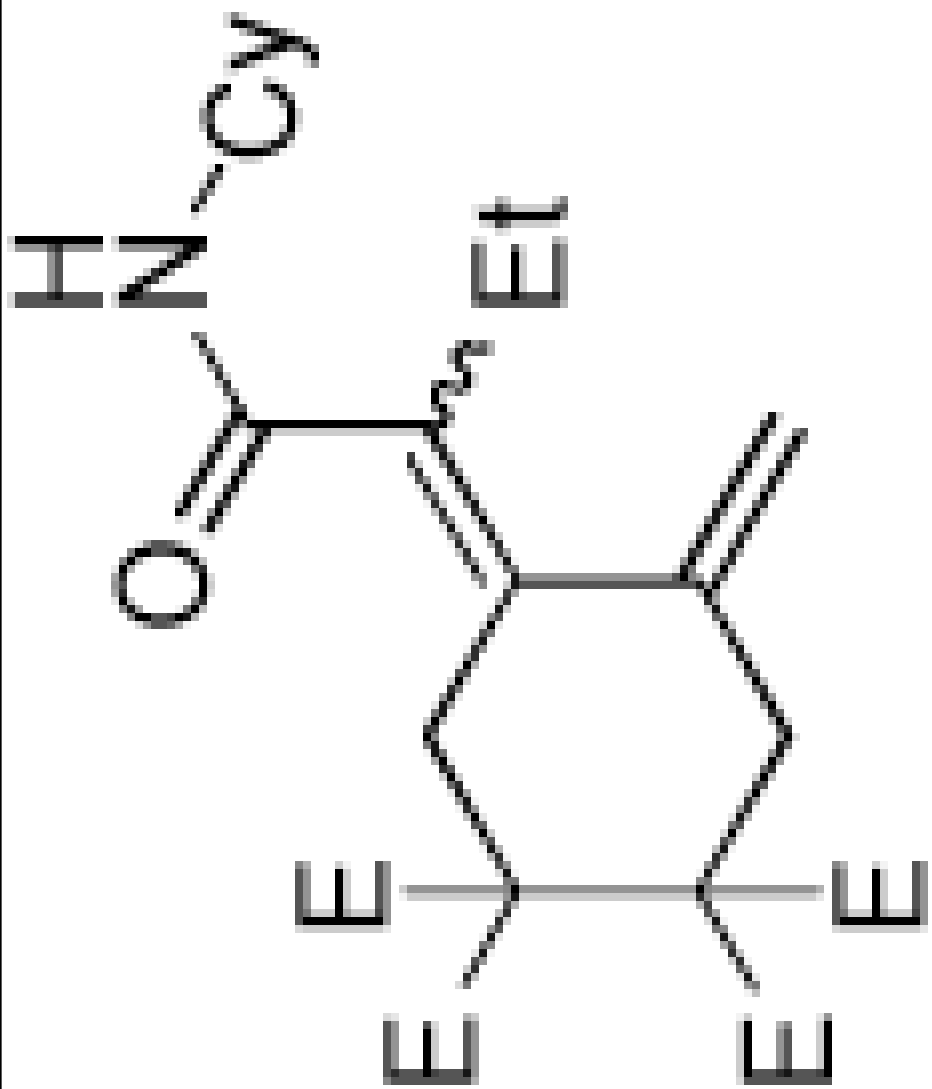
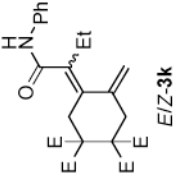
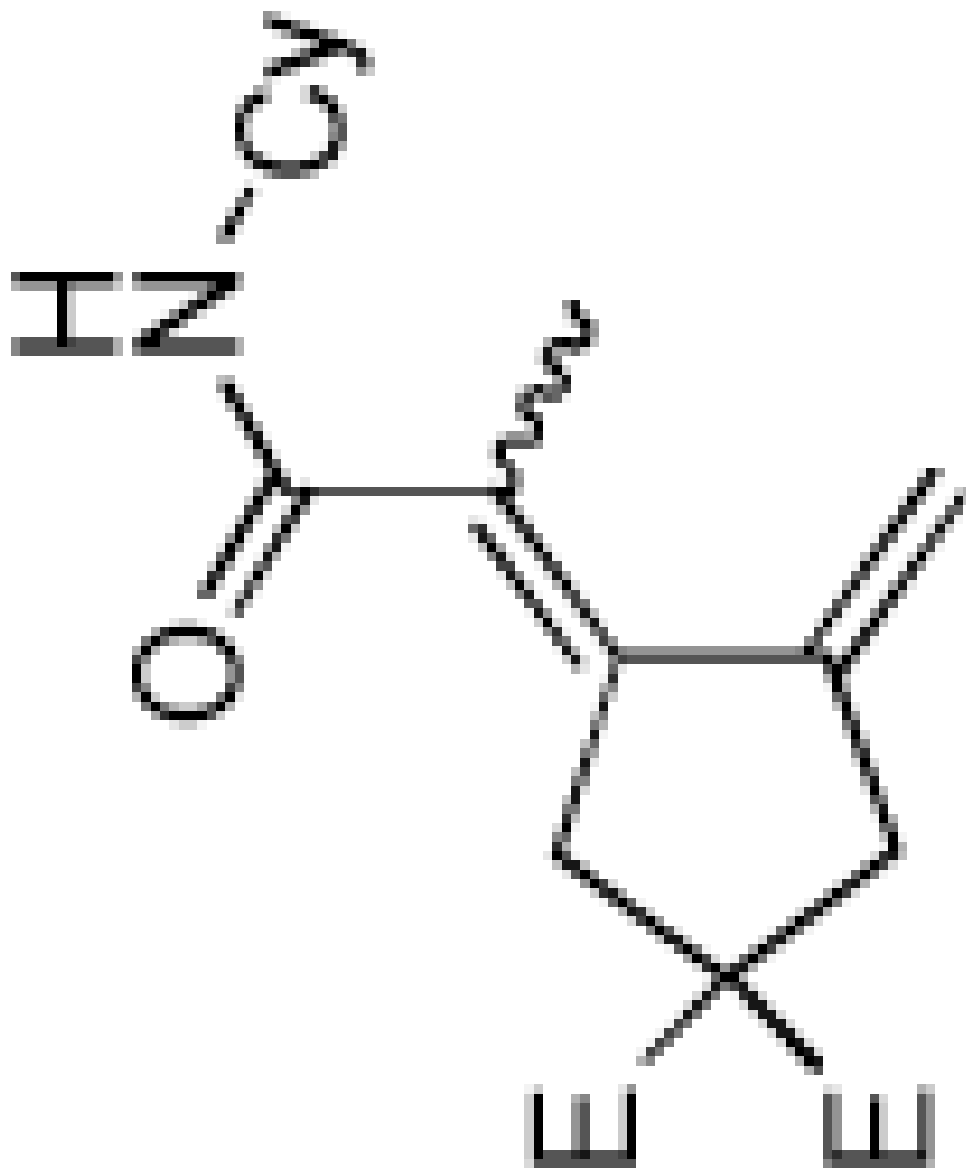
2:1 80 °C  
hReaction conditions: 1 equiv **1a**, 1 equiv **2**.<sup>a</sup>Determined by <sup>1</sup>H-NMR,<sup>b</sup>isolated yields, average of 2 runs

Table 3

isocyanate	<i>E, Z</i> products	<i>E:Z</i> ratio <sup>a</sup> % yield <sup>b</sup>
CyNCO 2a		4:1 89 <sup>c</sup>
b	E/Z-3j	

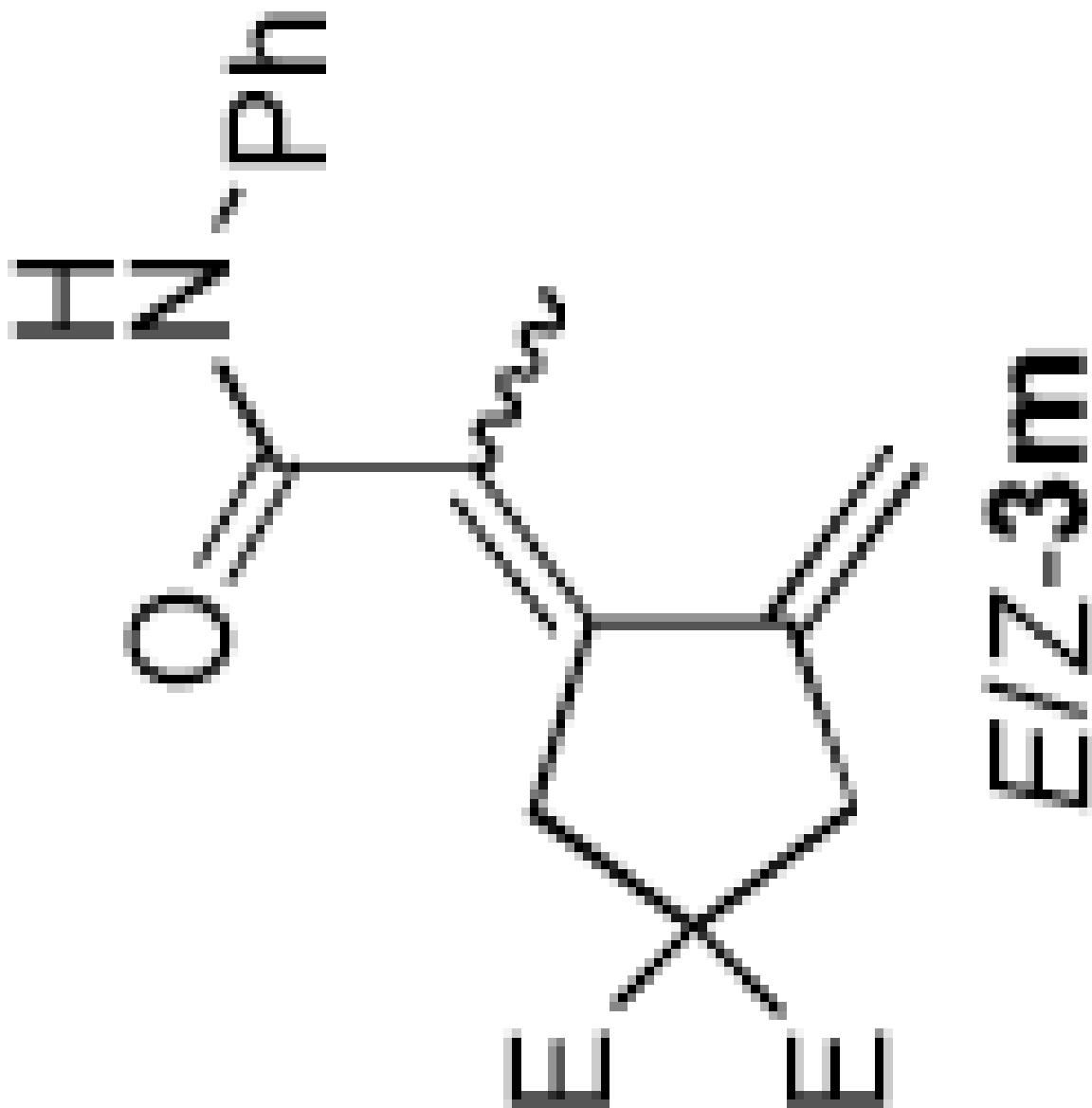
isocyanate	<i>E, Z</i> products	<i>E:Z</i> ratio <sup>d</sup> % yield <sup>b</sup>
PhNCO <b>2b</b>		4:1 84 <sup>d</sup>

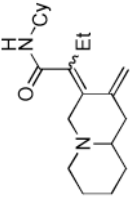
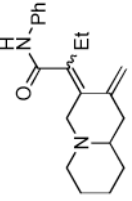
*E:Z ratio*<sup>d</sup>, yield<sup>b</sup>4:1 65<sup>c</sup>*E, Z products*

E/Z-31

isocyanate

2a

*E:Z ratio*<sup>d</sup>, yield<sup>b</sup>4:1 72<sup>f</sup>*E, Z products*

isocyanate	<i>E, Z</i> products	<i>E:Z</i> ratio <sup>d</sup> , yield <sup>b</sup>
2a	 $E/Z$ -3n	1.4:1    72 <sup>f</sup>
2b	 $E/Z$ -3o	1.4:1    72 <sup>f</sup>
2a/2b	nd	—    —