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Selectivity in Nickel-Catalyzed Rearrangements of Cyclopropylen-ynes

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Transition metal-catalyzed isomerization and rearrangement reactions of unsaturated systems provide rapid access to important heterocyclic and carbocyclic motifs. Toward this end, a variety of metal-catalyzed rearrangements have been developed over the past decade.[1] We recently discovered that the combination of Ni(0) and a sterically hindered N-heterocyclic carbene (NHC) effectively catalyzed the isomerization of vinyl cyclopropanes (VCPs) under mild conditions to afford cyclopentenes in excellent yields.[2] By tethering an alkynyl moiety to the VCP, we found that Ni/NHC systems also catalyze a rearrangement reaction to afford three different heterocyclic-based structures, two of which are distinct from those obtained employing Rh- and Ru-based catalysts.[3] Moreover, a single product can be generated selectively when an *N*-alkyl NHC is employed.

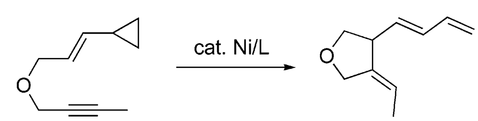
The Ni-catalyzed rearrangement of [(1*E*)-3-(2-butynyloxy)-1-propenyl]cyclopropane (**1a**) was investigated, and a variety of tertiary phosphines and NHCs[4] were explored as potential ligands (eq 1, Table 1). No rearrangement was observed in the absence of ligand or when tertiary phosphines were added as ligands (entries 1−4). Interestingly, smooth conversion of the cyclopropylen-yne **1a** was observed when an NHC was employed (entries 6−15). Furthermore, cyclopentane **2a** possessing a diene substituent was formed as the sole heterocyclic product.[5] Although almost every NHC screened ultimately afforded product **2a** in excellent yield (entries 6−17), rates were fastest with SIPr (entry 14). For example, **2a** was observed in 86, 76, and 89% after only half an hour at room temperature when I*t*Bu, IPr, and SIPr were employed, respectively (entries 8, 10, and 12). Increasing the Ni:L ratio had no significant effect on yield (entries 13−15, Table 1). In addition, toluene, benzene, pentane, THF, and ether were equally effective solvents.

Our initial investigations revolved around rearrangements catalyzed by the combination of $Ni(COD)_2$ and SIPr since rates of reaction were fastest with this system. Interestingly, as shown in Table 2, the size of the substituent on the alkyne (R) had a significant effect on the nature of the heterocyclic product that formed. Specifically, when R was small (e.g., R = Me (**1a**), entry 1), the expected cyclopentane product (**2a**) was formed exclusively. However, to our surprise, cyclopentanes **2b** and **2c** were not the sole rearrangement products from substrates **1b** and **1c** (entries 2 and 3). Instead, a mixture of heterocycles was obtained. This mixture included the expected cyclopentane (**2b** and **2c**) in addition to a bicyclic seven-membered ring (**3b** and **3c**). Furthermore, when R was large (e.g., R = *t*-Bu (**1d**) or TMS (**1e**), entries 4 and 5), isomerized seven-membered rings (**4d** and **4e**) were the sole products and were obtained in good yields.

A mechanism that diverges at a common intermediate and may account for the product distributions is shown in Scheme 1.[6] Reaction between the Ni catalyst and cyclopropylen-yne **1** would ultimately afford eight-membered intermediate **6**.[7,8] β-Hydride elimination and reductive elimination would afford cyclopentane product **2**. In contrast, if both the ligand and R are large, β-hydride would be inhibited and direct reductive elimination would yield seven-membered ring **3**. Product **4** would arise from further isomerization of **3**.[9]

Gratifyingly, we discovered the cyclopentane product (**2**) can be prepared *selectively* from cyclopropylen-yne substrates, regardless of substituent size (e.g., R), when I*t*Bu[10] was employed (eq 3). As shown in Table 3, cyclopentene products (**2a**−**d**, entries 1−4) were formed exclusively under mild conditions. As expected, the Ni/NHC catalyst system tolerated both amino (**8**) and ester (**10**)

Table 1. Ni-Catalyzed Rearrangement of Cyclopropylen-yne **1**[a]

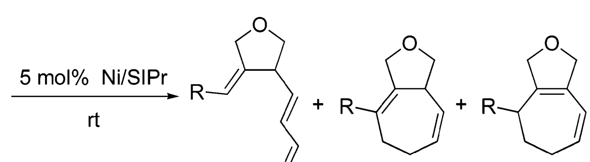


1a **2a** (1)

entry	L	Ni:L	time (h)	% conv. of **1a**[b]	% **2a**[b]
1	none	n/a	12	0	0
2	PPh_3	1:1	12	23	0
3	PCy_3	1:1	12	100	0
4	P*t*Bu_3	1:1	12	100	0
5	ICy	1:1	2	0	0
6	IAd	1:1	2	73	65
7	IMes	1:1	2	100	72
8	I*t*Bu	1:1	0.5	88	86
9	I*t*Bu	1:1	2	100	89
10	IPr	1:1	0.5	100	76
11	IPr	1:1	2	100	84
12	SIPr	1:1	0.5	100	89
13	SIPr	1:1	2	100	91
14	SIPr	1:2	0.5	100	86
15	SIPr	1:3	0.5	100	89

[a] Reaction conditions: 5 mol % $Ni(COD)_2$, toluene, room temperature. [b] Determined by GC using naphthalene as an internal standard.

Table 2. Product Distribution in the Ni-Catalyzed Rearrangement of **1**[a]

1 

2 **3** **4** (2)

entry	substrate	**2**:**3**:**4**[b]	% yield[c]
1	R = Me (**1a**)	1:0:0	54% (**2a**)
2	R = Et (**1b**)	3:2:0	34% (**2b**) 27% (**3b**)
3	R = *i*-Pr (**1c**)	1:2:0	28% (**2c**) 38% (**3c**)
4	R = *t*-Bu (**1d**)	0:0:1	82% (**4d**)
5	R = TMS (**1e**)	0:0:1	88% (**4e**)

[a] Reaction conditions: 5 mol % $Ni(COD)_2$, 5 mol % SIPr, toluene, ambient temperature. [b] Determined by GC using naphthalene as an internal standard. [c] Isolated yield (average of two runs).

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Scheme 1. Proposed Mechanism for the Rearrangement of **1**

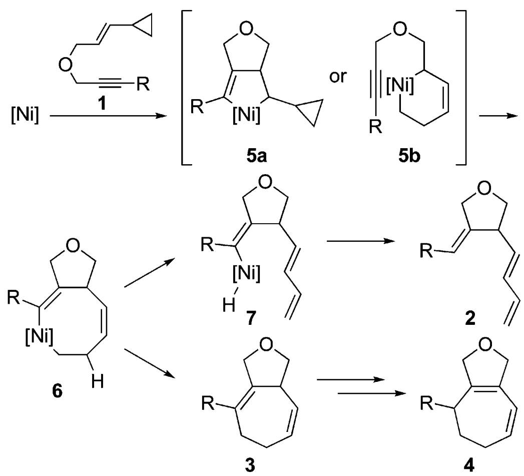
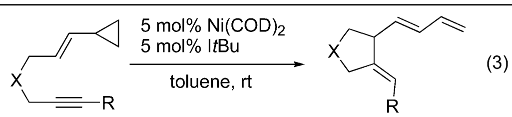
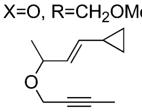
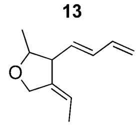
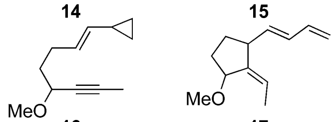
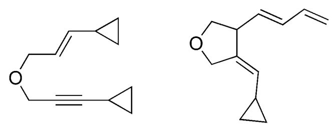


Table 3. Selective Formation of Cyclopentanes[a]



Entry	Cyclopropylen-yne	Product	% Yield[b]
1	X=O, R=Me (**1a**)	**2a**	54%
2	X=O, R=Et (**1b**)	**2b**	52%
3	X=O, R=*i*-Pr (**1c**)	**2c**	65%
4	X=O, R=*t*-Bu (**1d**)	**2d**	79%
5	X=C(CO_2Me)$_2$, R=Me (**8**)	**9**	71%[c]
6	X=NTs, R=Me (**10**)	**11**	86%[c]
7	X=O, R=CH_2OMe (**12**)	**13**	64%
8	 **14**	 **15**	61%
9	 **16**	**17**	55%[c,d]
10	 **18**	**19**	61%

[a] Reaction conditions: 5 mol % Ni(COD)$_2$, 5 mol % I*t*Bu, toluene, room temperature. [b] Isolated yields (average of two runs). [c] SIPr was used as the ligand instead of I*t*Bu. [d] Reaction was run at 40 °C.

functionality (entries 5 and 6). Furthermore, internal substitution did not effect the rearrangement (entries 8 and 9). Interestingly, rearrangement of **18** afforded a tetrahydrofuran product (**19**) possessing a VCP moiety that resisted further isomerization to a spirocyclopentane (entry 10).[11]

We have discovered a variety of conditions based on Ni/NHC systems for the rearrangement of cyclopropylen-ynes to afford cyclopentane- and cycloheptene-based heterocycles. However, the use of I*t*Bu led to the selective formation of the cyclopentane products. Investigations focused on developing protocols for selective cycloheptene formation and understanding the mechanistic details of the rearrangements are currently underway.

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Supporting Information Available: Detailed experimental procedures and compound characterization data are available (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Rearrangements proceeded smoothly in the presence of a variety of radical traps (e.g., 2,6-di-*tert*-butyl-4-methylphenol, 1,4-cyclohexadiene, phenyl disulfide, glavinoxyl).

(7) It is unclear at this time whether **6** would result from **5a** or **5b**. A variety of Ni compounds are known to catalyze cycloaddition reactions of enynes via initial oxidative coupling between an alkene and alkyne (see ref 8). Thus, a similar pathway could led to the formation of **6** via intermediate **5a**. Indeed, a similar mechanism has been proposed for analogous Rh- and Ru-catalyzed chemistry (see ref 3). However, we recently discovered that the Ni/NHC catalyst system mediates the isomerization of VCPs. Consequently, **6** may be derived from the initial isomerization of the VCP (**5b**) and subsequent insertion of the alkyne (see ref 2a).

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(9) It is possible that isomerization to form **4** occurs via the generation of a Ni−H complex (see ref 5). Indeed, the addition of catalytic amounts of HBF_4 (10 mol %) to Ni/I*t*Bu-catalyzed reactions of **1d** led to complete conversion and formation of **4d**. We are currently investigating the isomerization mechanism.

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(11) When Ni/SIPr was used as the catalyst, further isomerization occurred to give a mixture of products. As shown in Table 1, Ni/I*t*Bu is a less active catalyst system than Ni/SIPr, which allows for the selective formation of **19**.

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