Rearrangement

Highly Active Nickel Catalysts for the Isomerization of Unactivated Vinyl Cyclopropanes to Cyclopentenes**

*Gang Zuo and Janis Louie**

Since its discovery in 1959, the rearrangement of vinyl cyclopropanes (VCPs) has attracted considerable attention.[1] Transformations of this type yield substituted cyclopentenes, which are a common structural motif in many biological systems.[2] Typical conditions originally involved high-temperature pyrolysis or photolysis but these ultimately hampered the reaction's utility.[3] Approximately two decades later, reaction conditions were vastly improved with the development of odd-electron-promoted isomerizations, which remain some of the mildest to date.[4] Unfortunately, activated substrates (for example, with CO_2R, OCO_2R, OR, or Ph moieties) are required to facilitate the reaction and this ultimately necessitates additional synthetic steps.

Transition metals (Ni, Pd, Rh, Cu, Cr, Mo, and Fe) have also been reported to catalyze rearrangements of VCP.[5] However, these protocols do not offer significant improvement over the methods described above. They require high temperatures (60–100 °C) and are also generally limited to activated VCPs.[6] The electron-withdrawing substituents are postulated to increase oxidative addition or stabilize the anionic ring-opened intermediate that presumably forms from nucleophilic attack on the olefin. Alternatively, extended conjugated systems such as cyclopropyl dienes have been used but their success is believed to be at least partially a consequence of the high affinity (that is, chelation) of olefins for (Group X) metals.[6]

Despite the limited information available on the mechanism of metal-mediated VCP isomerizations, we envisioned that a highly reduced metal could accelerate the overall reaction and lead to a catalytic system with an increased range of suitable substrates. A metal with increased electron density would possess a higher nucleophilicity and would therefore be more likely to attack the olefinic moiety of the VCP. The metal would also be expected to facilitate oxidative ring opening of the cyclopropane ring. In either case, stabilization of the resulting positively charged metal intermediate would be key to promoting the reaction. With these requirements in mind, we chose to examine nitrogen-heterocyclic carbenes (NHCs) as possible ligands for nickel-catalyzed isomerizations of VCPs since these ligands are known to display an enhanced sigma-donating ability relative to their phosphane and amine counterparts and they possess a high affinity for nickel.[7] Herein, we report that the combination of Ni^0 with a sterically hindered NHC ligand catalyzes the isomerization of a variety of activated *and* unactivated VCPs under mild conditions to afford the respective cyclopentenes in good yields. When this result is combined with recent developments in the synthesis of VCPs,[8] we anticipate that it will be a powerful technique for the preparation of five-membered carbocyclic structures.

The isomerization of 3-cyclopropylbut-3-enylbenzene (**1**) was chosen as the model reaction and a variety of conditions were screened [Eq. (1), Bn = benzyl; cod = cyclo-1,5-octadiene, Table 1]. $[Ni(cod)_2]$ was chosen as the source of Ni^0 and was combined with IPr to form the NHC-ligated Ni catalyst in situ.[9] Quantitative formation of 2-(cyclopent-1-enyl)ethylbenzene (**2**) was achieved at room temperature with catalyst loadings as low as 1 mol % Ni (2 mol % IPr). As expected, the reaction time increased as the catalyst loading was lowered, however a slightly increased reaction temperature (50 °C) led to higher rates of reaction (1 h versus 12 h). Isomerizations

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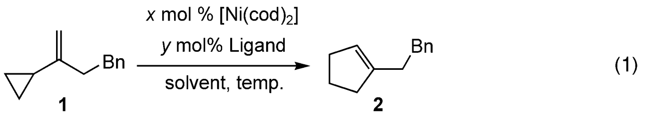


(1)

Table 1: Optimization of a nickel-catalyzed isomerization of 3-cyclopropyl-but-3-enylbenzene (**1**).[a]

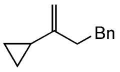
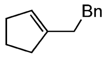
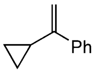
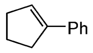
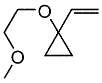
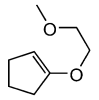
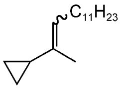
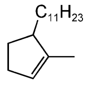
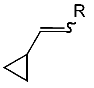
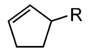
$[Ni(cod)_2]$ [mol%]	Ligand (mol%)	Solvent	*T*	*t* [h]	Yield [%][b]
5	IPr (10)	toluene	RT	4	100
3	IPr (6)	toluene	RT	6	100
1	IPr (2)	toluene	RT	12	100
1	IPr (2)	toluene	50 °C	1	100
1	IPr (2)	benzene	RT	24	100
1	IPr (2)	THF	RT	14	100
1	IPr (2)	dioxane	RT	14	100
1	IPr (2)	CH_2Cl_2	RT	24	N.R.
1	IPr (2)	CH_3CN	RT	24	N.R.
1	IPr (2)	hexane	RT	6	100
1	IPr (2)	pentane	RT	10	100
1	IPr (1)	pentane	RT	10	41
1	IPr (3)	pentane	RT	10	37
5	IMes (10)	pentane	RT	12	49
5	PCy_3 (10)	toluene	100 °C	24	N.R.
5	none	toluene	RT	4	N.R.
0	IPr (2)	toluene	RT	24	N.R.

[a] IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene, IMes = 1,3-bis-(1,3,5-trimethylphenyl)imidazol-2-ylidene, Cy = cyclohexyl, THF = tetrahydrofuran, N.R. = not recorded. [b] Determined by GC with naphthalene as an internal standard.

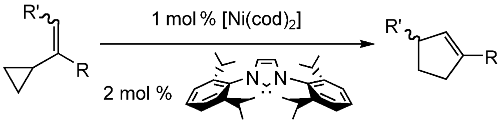
were facile in a variety of hydrocarbon solvents but were completely inhibited in acetonitrile and dichloromethane. The optimum Ni:IPr ratio was determined to be 1:2. The use of larger or smaller amounts of IPr relative to Ni resulted in lower yields.[10] For comparison, 1,3-bis-(1,3,5-trimethylphenyl)imidazol-2-ylidene (IMes) was also investigated as an NHC ligand in the reaction. However, relatively lower yields and reaction rates were observed with IMes than with the IPr ligand under identical conditions (49% versus 100%, respectively). A previously reported phosphane-based ligand (that is, PCy_3) afforded no cyclopentene products even at elevated temperatures (100 °C) and after extended periods of time (24 h). As expected, no product was formed in the absence of either ligand or $[Ni(cod)_2]$.

As shown in Table 2, a variety of VCPs were subjected to the optimized nickel-catalyzed isomerization reaction conditions described above [Eq. (2), 1 mol% $[Ni(cod)_2]$, 2 mol% IPr). VCPs possessing an electron-withdrawing group, heteroatom, or phenyl group on the cyclopropane ring underwent rapid isomerization and afforded high yields of the corresponding cyclopentene. Similarly, 1,1-disubstituted olefins reacted efficiently to afford the corresponding trisubstituted cyclopentenes. Furthermore, although slightly elevated temperatures were necessary, simple trisubstituted olefins were successfully isomerized as well. In contrast, the reaction with 1,2-disubstituted olefins possessing either *cis* or *trans* olefinic geometries was generally sluggish, even under more forcing conditions (100 °C).

Table 2: Nickel-catalyzed isomerization of various vinyl cyclopropanes.[a]

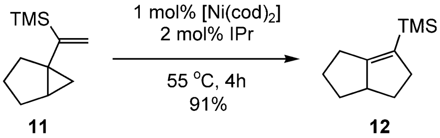
Substrate	Product	*T*	*t* [h]	Yield [%][b]
		RT	12	93
		RT	1	96
		RT	2	93
		60 °C	12	94
				
9a, R = Ph	**10a**	60 °C	12	92
9b, R = CH_2OBz	**10b**	100 °C	12	–[c]
9c, R = TMS	**10c**	100 °C	12	N.R.
9d, R = $(CH_2)_2Ph$	**10d**	100 °C	12	N.R.

[a] Performed with 1.0 mol% $[Ni(cod)_2]$, 2.0 mol% IPr, and 0.10 M substrate in toluene, benzene, or hexanes. Bz = benzoyl, TMS = trimethylsilyl. [b] Yields of isolated products (average of at least two runs). [c] Complete conversion of VCP substrate was observed but no cyclopentene product was formed. N.R. = no reaction.



(2)

A cyclopentene possessing a bicyclic framework found in a variety of natural products[2] was prepared by subjecting the substituted VCP **11** to the nickel-catalyzed isomerization reaction described above [Eq. (3)]. The resulting cyclopentene **12** was isolated in 91% yield after 4 h (55 °C). Importantly, compound **12** possesses an exocyclic, tetrasubstituted double bond containing a trimethylsilyl group which may be used for further derivatization.



(3)

Ni^{II} catalysts in conjunction with trialkylaluminum reagents are known to mediate an alternative isomerization pathway that yields dienes from unactivated VCPs.[11] A key step is the insertion of the VCP olefinic moiety into a nickel hydride bond. To determine whether nickel hydrides were relevant to the $[Ni(IPr)_2]$-catalyzed reaction described above, VCP **1** was subjected to catalytic amounts of $[Ni(IPr)_2]$ in the presence of acids that are known to form nickel(II) hydrides.[12] No cyclopentene was formed and the starting material was quantitatively recovered when one equivalent (relative to Ni) of HCl (in dioxane) was added. However, the addition of HBF_4 (in diethyl ether) led to the complete consumption of VCP **1**, but neither diene nor cyclopentene was detected. (The product of this reaction has been elusive thus far.) Nevertheless, these results suggest that the VCP isomerizations were catalyzed by an Ni^0 species and do not involve nickel hydrides.

Although a number of nitrogen-heterocyclic carbenes are indefinitely stable under an inert atmosphere, they can be easily generated in situ from the appropriate precursor salt and base.[13] Such a method has been used in a variety of metal-mediated reactions, including olefin metathesis,[14] the Suzuki–Miyaura reaction,[15] the Buchwald–Hartwig amination,[16] and the Kumada–Corriu reaction.[17] Similarly, VCP **1** was subjected to catalytic amounts of $[Ni(cod)_2]$ (5 mol%), $IPrBF_4$ (10 mol%), and KO*t*Bu (10 mol%) in pentane. A quantitative yield of cyclopentene product **2** was observed by gas chromatography after only 12 h at room temperature.

In conclusion, we have developed a mild and efficient protocol for the preparation of cyclopentenes from the isomerization of vinyl cyclopropanes. The reaction employs catalytic amounts of Ni^0 and a nitrogen-heterocyclic carbene ligand. Most importantly, activated VCPs are not required for efficient transformation. We are currently working toward expanding the substrate scope, enhancing the catalyst performance, and understanding the mechanism of this reaction.

Experimental Section

Representative procedure: In a dry-box, VCP **1** (200 mg, 1.2 mmol) was added to an oven-dried screw-cap vial equipped with a magnetic stirrer bar and was subsequently dissolved in pentane (1.5 mL). Alternatively, the reaction may be performed outside of a drybox by adding VCP **1** and dry, degassed pentane through a syringe to an oven-dried flask (which has previously been evacuated and filled with N_2) equipped with a septum, stirrer bar, and gas-adapter. A solution of $[Ni(cod)_2]$ (3 mg, 0.01 mmol) and IPr (8 mg, 0.02 mmol) in pentane (0.5 mL) that had previously equilabrated for 12 h was then added and the reaction vessel was sealed appropriately. The resulting dark greenish-black solution was then stirred at room temperature until the starting material was completely consumed (as determined by GC). The products were then purified by chromatography on silica gel (with pentane as the eluent).

Further experimental details are available in the Supporting Information.

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