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Cu(I)-Catalyzed Cycloguanidination of Olefins

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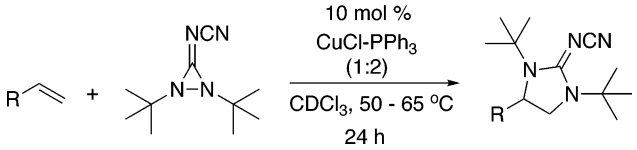
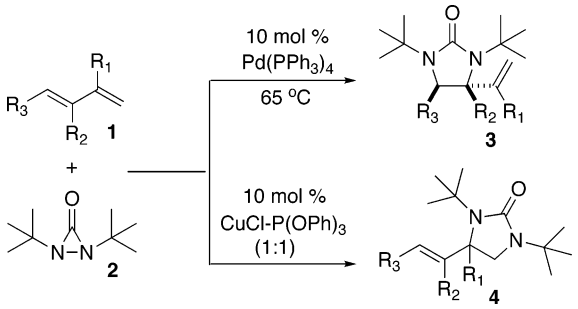
ABSTRACT



This paper describes a novel cycloguanidination process using CuCl as catalyst and diaziridinimines as the nitrogen source. A variety of conjugated dienes, trienes, and terminal olefins can be effectively diaminated under mild reaction conditions. For dienes and trienes, the reaction occurs at the terminal double bond with high regioselectivity.

Cyclic guanidines are present in a variety of biologically active compounds,[1] including massadine (geranylgeranyltransferase type I inhibitor),[2] palau'amine (antibiotic, cytotoxic, and immunosuppressive agent),[3] streptolidine lactam (a component of the streptothricin antibiotics),[4] and mannopeptimycins (antibiotic agents against drug-resistant bacteria).[5] Cyclic guanidines are normally prepared[1] by cyclization of vicinal diamines[6] or guanidines,[7] and by cycloaddition of aziridines and carbodiimides.[8] Cycloguanidination of olefins provides a valuable approach to cyclic guanidines, yet it needs to be further developed.[9] Recently, we reported a Pd(0)-[10,11] and a Cu(I)-catalyzed[12] regio- and stereoselective diamination of conjugated dienes and trienes using di-*tert*-butyldiaziridinone (**2**)[13,14] as the nitrogen source (Scheme 1)

Scheme 1



as well as Cu(I)-catalyzed[15] diamination of activated terminal olefins using di-*tert*-butylthiadiaziridine 1,1-dioxide as the

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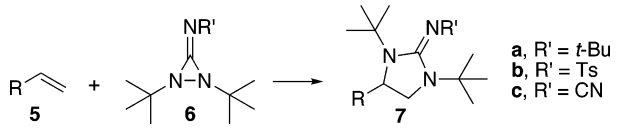
nitrogen source.[16,17−22] In an effort to expand the related diamination processes, we have been investigating whether diaziridinimines can be used as the nitrogen source to form cyclic guanidines from olefins (Scheme 2). Herein we report

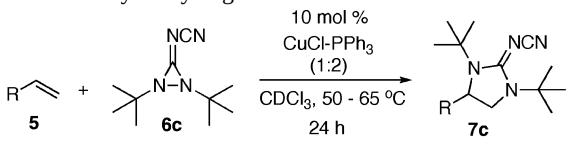
Scheme 2

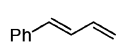
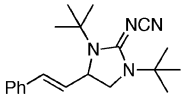
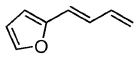
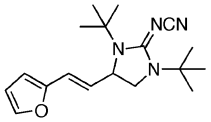
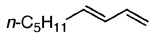
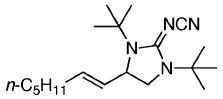
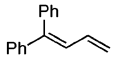
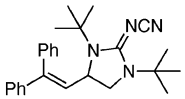
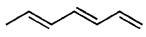
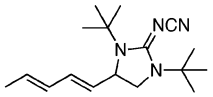
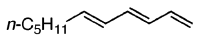
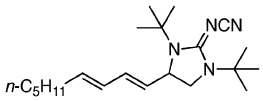
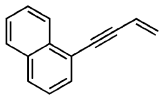
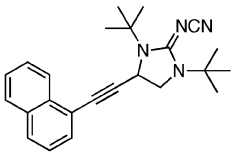
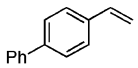
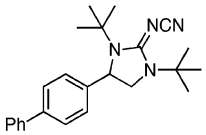
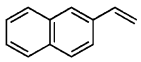
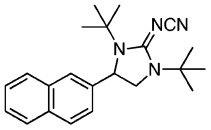
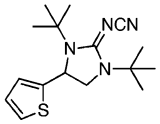


our preliminary efforts on this subject.

Initial studies were carried out using 1-phenyl-1,3-butadiene as the substrate and diaziridinimines **6a**−**c**[23] as the nitrogen source. Little guanidine product was detected with $Pd(PPh_3)_4$ as catalyst. When CuCl-P(*n*-Bu)$_3$ was used as the catalyst, no diamination reaction was observed with diaz-

Table 1. Catalytic Cycloguanidination of Olefins[a]



entry	substrate (**5**)	product (**7c**)	yield (%)[b]
1	 **5a**		86
2	 **5b**		70
3	 **5c**		50
4	 **5d**		81
5	 **5e**		73
6	 **5f**		78
7	 **5g**		54
8	 **5h**		48
9	 **5i**		62
10	 **5j**		74

[a] All reactions were carried out with olefin (0.2 mmol), 1,2-di-*tert*-butyl-3-(cyanimino)diaziridine (**6c**) (0.41 mmol), CuCl−PPh_3 (1:2) (0.02 mmol) in $CDCl_3$ (0.1 mL) at 50 °C under argon for 24 h unless otherwise stated. For entries 7−10, the reactions were carried out at 65 °C. [b] Isolated yield based on olefin.

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iridinimines **6a** and **6b**. However, good conversion was obtained with **6c** to give the desired cyclic guanidine product. Under the reaction conditions, diaziridinimine **6a** with an electron-donating *tert*-butyl group remained unreacted, but **6b** with a strong electron-withdrawing Ts group decomposed rapidly. This indicates that the R substituent on iminodiazaridines **6** has a significant impact on the reaction outcome, and the cyano group appears to be an effective substituent for the reaction. After additional optimization of conditions, the reaction was further improved using 10 mol % of CuCl-PPh_3 (1:2) as catalyst at 50−65 °C in $CDCl_3$. As shown in Table 1, the reaction can be extended to additional olefins.[24] Dienes and trienes are effective substrates, and the reaction occurred highly regioselectively at the terminal double bond (Table 1, entries 1−6). Other regioisomers were barely detectable by ^{1}H NMR of the crude reaction mixture. Enyne and arylethylenes can also be guanidinated but with relatively lower reactivity (the X-ray structure of **7ci** is shown in Figure 1). However, terminal olefins such as 1-octene and ethyl

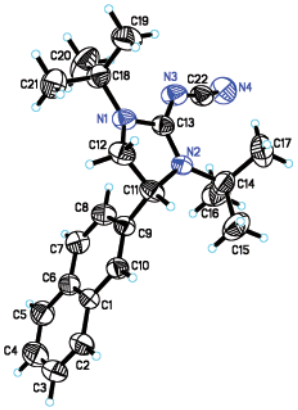
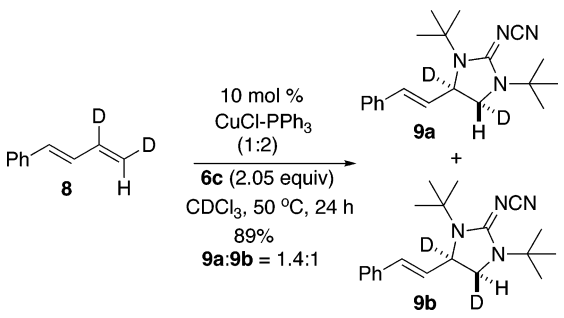


Figure 1. X-ray structure of compound **7ci**.

acrylate are not effective substrates under the current reaction conditions.

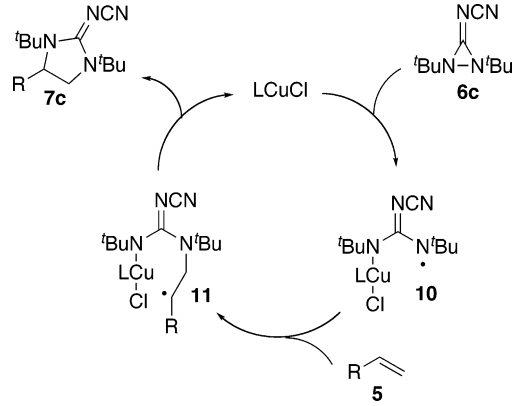
When deuterated diene **8** was subjected to the reaction conditions, a mixture of two isomers (**9a** and **9b**) was

Scheme 3



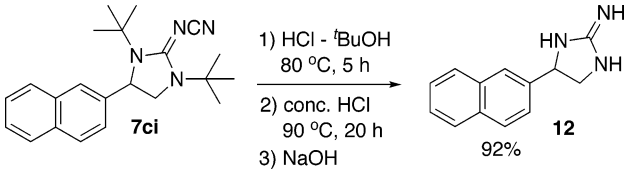
obtained (Scheme 3). While a precise reaction mechanism awaits further study, the cycloguanidination is consistent with the previously proposed catalytic mechanism,[12,15] proceeding via the homolytic cleavage of the N−N bond of diaziridinimine **6c** by CuCl, followed by the addition of the resulting nitrogen radical **10**[25−28] to olefin **5** and the subsequent C−N bond formation and regeneration of CuCl catalyst (Scheme 4).

Scheme 4. Proposed Catalytic Cycle for Cycloguanidination



The deprotection of the resulting cyclic guanidines was investigated with compound **7ci** (Scheme 5). Both the *tert*-

Scheme 5



butyl and the cyano groups were smoothly removed with HCl to give guanidine **12** in good overall yield after neutralization with NaOH.[29]

In summary, a variety of conjugated dienes, trienes, and terminal olefins have been effectively cycloguanidinated

(24) **A representative diamination procedure (Table 1, entry 1):** To a 1.5 mL vial equipped with a stir bar was added CuCl (0.002 g, 0.02 mmol) and triphenylphosphine (0.0104 g, 0.04 mmol). The sealed vial was evacuated and filled with Ar three times, followed by addition of $CDCl_3$ (0.05 mL). After the mixture was stirred at room temperature for 10 min, 1-phenyl-1,3-butadiene (**5a**) (0.026 g, 0.20 mmol) was added, followed by a solution of 1,2-di-*tert*-butyl-3-(cyanimino)diaziridine (**6c**) (0.080 g, 0.41 mmol) in 0.05 mL of $CDCl_3$ (for solid olefins, they were added together with CuCl). The reaction mixture was stirred at 50 °C for 24 h and purified by flash chromatography (silica gel, petroleum ether/ethyl acetate/triethylamine = 4:1:0.05 to 3:1:0.04) to give the diamination product **7ca** as a colorless oil (0.056 g, 86%).

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using CuCl as catalyst and 1,2-di-*tert*-butyl-3-(cyanimino)-diaziridine (**6c)** as nitrogen source under mild reaction conditions, providing various cyclic guanidine derivatives which are present in many biologically active compounds.[1−7] For dienes and trienes, the reaction occurs regioselectively at the terminal double bond. The cycloguanidination is likely to proceed via a nitrogen radical intermediate. Further studies on the reaction mechanism, different catalysts, and nitrogen sources as well as expansion of the substrate scope and development of an asymmetric process are currently underway.

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Supporting Information Available: The cycloguanidination and deprotection procedures, the characterization of cyclic guanidine products, and the X-ray data of compound **7ci** along with the ^1H and ^{13}C NMR spectra of **7c**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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