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# Cu(I)-Catalyzed Diamination of Disubstituted Terminal Olefins: An Approach to Potent $NK_1$ Antagonist

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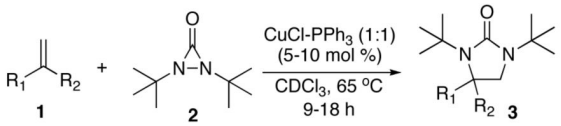
## Abstract




This paper describes a diamination process using di-*tert*-butyldiaziridinone as nitrogen source and CuCl as catalyst. A wide variety of disubstituted terminal olefins can be efficiently diaminated in good yields under mild condition. This diamination process was used to synthesize potent $NK_1$ antagonist Sch 425078.

Diamination of olefins provides an effective approach to vicinal diamines, which are biologically and chemically important functional moieties.[1] Various metal-mediated[2,3] and metal-catalyzed[4-6] diaminations have been developed. Recently, we have reported the Pd(0)- and Cu(I)-catalyzed regioselective diamination of conjugated dienes and trienes[7,8,9] as well as the dehydrogenative diamination of terminal olefins[10,11] using di-*tert*-butyldiaziridinone,[13,14] diaziridinimine,[15] or di-*tert*-butylthiadiaziridine 1,1-dioxide[16] as the nitrogen sources. The Cu(I)-catalyzed diamination process has also been extended to activated mono-substituted terminal olefins such as styrenes, enynes, enol ether etc.[9,12] Considering the fact that 4,4-disubstituted-2-imidazolidinones (Figure 1) have been shown to be potent $NK_1$ antagonists,[17] and in conjunction with our efforts to expand the diamination scope, we have investigated the diamination of disubstituted simple terminal olefins using di-*tert*-butyldiaziridinone (**2**) as the nitrogen source (Scheme 1).[8] Herein, we wish to report our studies on this subject.

Initial studies were carried out using 2-phenylpropene as the substrate and di-*tert*-butyldiaziridinone (**2**) as the nitrogen source. When $Pd(PPh_3)_4$ was used as catalyst, only a trace amount of diamination product was observed. However, >95% conversion was obtained when the reaction was carried out with 5 mol % of CuCl-$PPh_3$ (1:1) in $CDCl_3$ at 65 °C.[18] As shown in Table 1, various 2-phenylpropenes with different substituents on the phenyl ring can be successfully diaminated in moderate to good yield (Table 1, entries 1-9).[19] 2-Isopropenylnaphthalene **1j** is also an effective substrate (Table 1, entry 10). Substrates with different alkyl substituents (such as ethyl, benzyl, and methoxymethyl groups) can also be diaminated in 55-71% yield (Table 1, entries 11, 12, 13, and 14). The diamination process can also be extended to α,β-unsaturated esters (Table 1, entries 15 and 16). However, dialkyl

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**Supporting Information Available:** The experimental procedures, the characterization of diamination products **3**, NOE studies of compound **4a**, and the $^1H$ and $^{13}C$ NMR spectra of compounds **3**, **4a**, **5a**, **6a**, and **9**-**14** along with the X-ray data of compound **14** (74 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

terminal olefins, such as 2-methyl-3-phenyl-1-propene, are not effective substrates for this diamination.

The deprotection of the diamination products was investigated with compound **3a** (Scheme 2). Treating **3a** with $CH_3SO_3H$ in hexane (1:10, v/v) at room temperature gave monodeprotected compound **4a** in 99% yield.[20] The structure of compound **4a** was confirmed by NOE analysis and X-ray structure of related compound **14** (Figure 2, Scheme 4). When the deprotection was carried out at 65 °C, both *tert*-butyl groups were smoothly removed in 85% yield. Free diamine **6a** can be obtained in 87% yield directly from **3a** by deprotection with concentrated HCl.[7c, 10]

The application of this catalytic diamination to the synthesis of potent $NK_1$ antagonist 4,4-disubstituted 2-imidazolidinone **Sch 425078**[17] is outlined in Scheme 3. Disubstituted terminal olefin **9** was readily prepared in 77% yield by reaction between α-bromomethylstyrene (**7**) and commercially available (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethanol using NaH as base. Diamination of olefin **9** with CuCl-$P(OPh)_3$ and di-*tert*-butyldiaziridinone (**2**) gave 4,4-disubstituted 2-imidazolidinones **10** and **11** in 35% and 30% yield respectively,[21] after flash chromatography (the less polar spot on the TLC corresponds to compound **10**). Removal of both *tert*-butyl groups of compound **10** provided compound **12** (**Sch 425078**) in 74% yield.

To further confirm the configuration of the diamination product **10**, one *tert*-butyl group was selectively removed using $CF_3CO_2H$ at room temperature to give compound **13**, which was converted to compound **14** with *n*-BuLi and benzoyl chloride[22] (Scheme 4). The structure of compound **14** was determined by X-ray analysis (Figure 2). The determination of the structure of monodeprotected product **13** supports the structure assignment of mono-deprotected compound **4a** in Scheme 2.

In summary, a variety of disubstituted terminal olefins have been effectively diaminated using CuCl as catalyst and di-*tert*-butyldiaziridinone as nitrogen source, which provides a rapid access to various 4,4-disubstituted-2-imidazolidinones.[23] In addition, the synthesis of 4,4-disubstituted-2-imidazolidinone **Sch 425078** (potent $NK_1$ antagonist) has been achieved in three steps using this diamination. The ability to selectively remove one or two protecting groups would provide opportunities to introduce different substituents on the nitrogens if desired. Future efforts will be devoted to the development of an asymmetric diamination process and its applications.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

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(18). When the CuCl-catalyzed diamination of 2-phenylpropene was carried out with di-*tert*-butylthiadiaziridine 1,1-dioxide or 1,2-di-*tert*-butyl-3-(cyanimino)diaziridine as the nitrogen source

under the previously reported conditions (refs. 9 and 12), only a small amount of diamination product or a messy mixtutre was obtained, respectively.

(19). 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), triphenylphosphine (0.0052 g, 0.02 mmol), and $CDCl_3$ (0.3 mL). After the mixture was stirred at room temperature for 10 min, 2-phenylpropene (1a) (0.047 g, 0.4 mmol) was added. The reaction mixture was warmed to 65 °C using an oil bath with stirring, and ditert-butyldiaziridinone (2) (0.136 g, 0.8 mmol) was added by syringe pump over 8 h. The reaction mixture was stirred at this temperature for an additional 1 h and purified by flash chromatography (silica gel, hexane/ether = 10/1) to give diamination product 3a as a white solid (0.105 g, 91%).

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(21). Diamination of olefin **9** with CuCl-$PPh_3$ (1:1) (10 mol %) in $CDCl_3$ at 65 °C for 10 h gave compound **10** in 30% yield and **11** in 33% yield. Diamination of **9** with CuCl-(*R*)-DTBM-SEGPHOS (2:1) (10 mol %)[8] in $CDCl_3$ at 65 °C for 10 h gave compound **10** in 32% yield and **11** in 29% yield.

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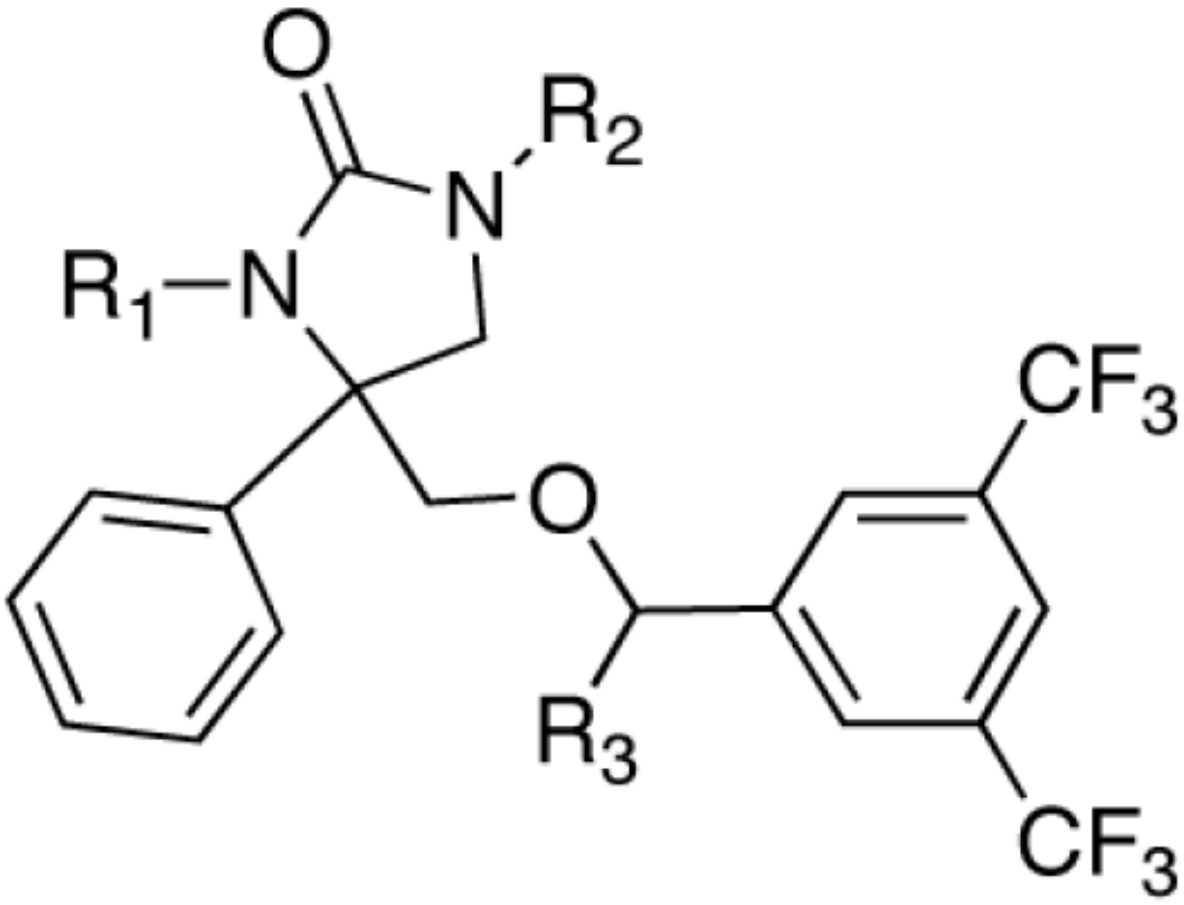
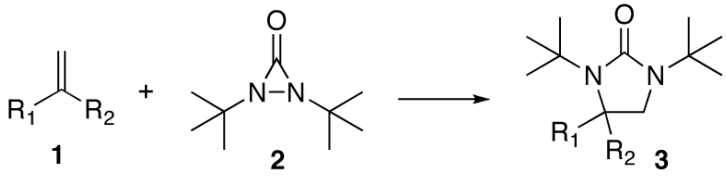
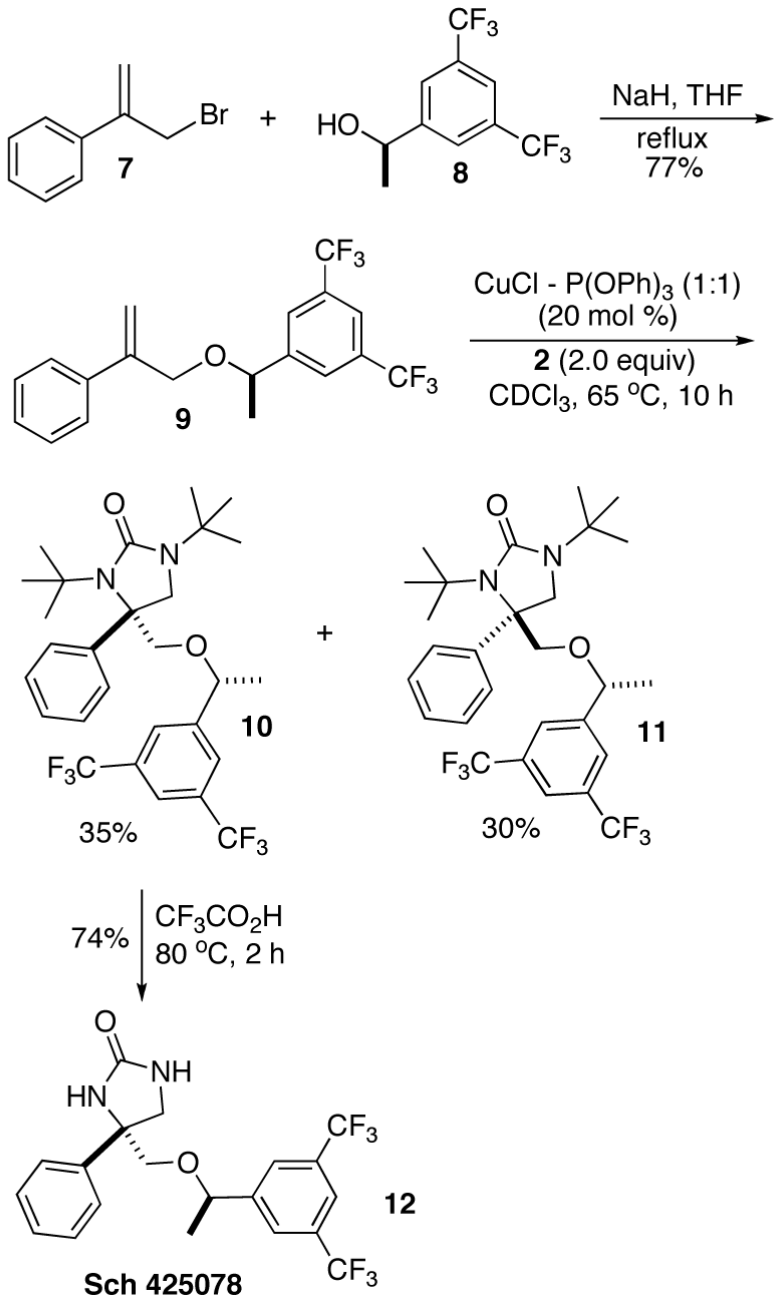



**Figure 1.**
$NK_1$ antagonists




**Scheme 1.**

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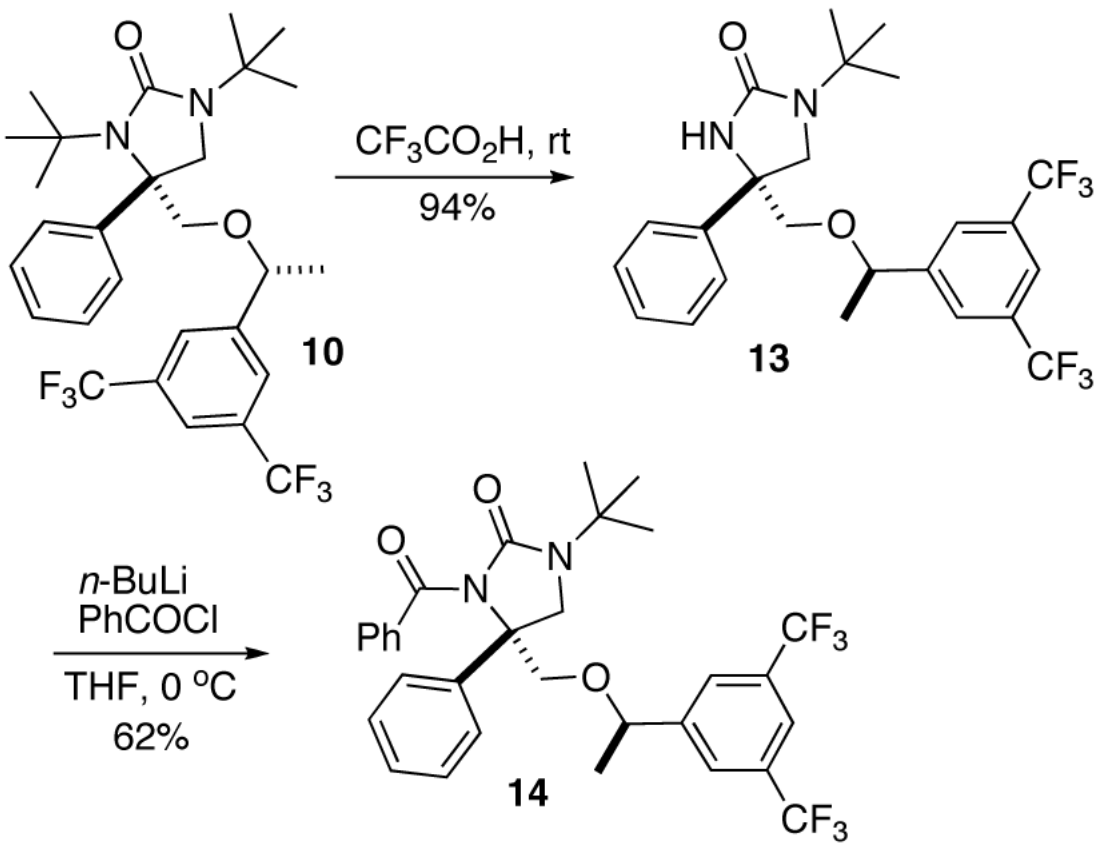


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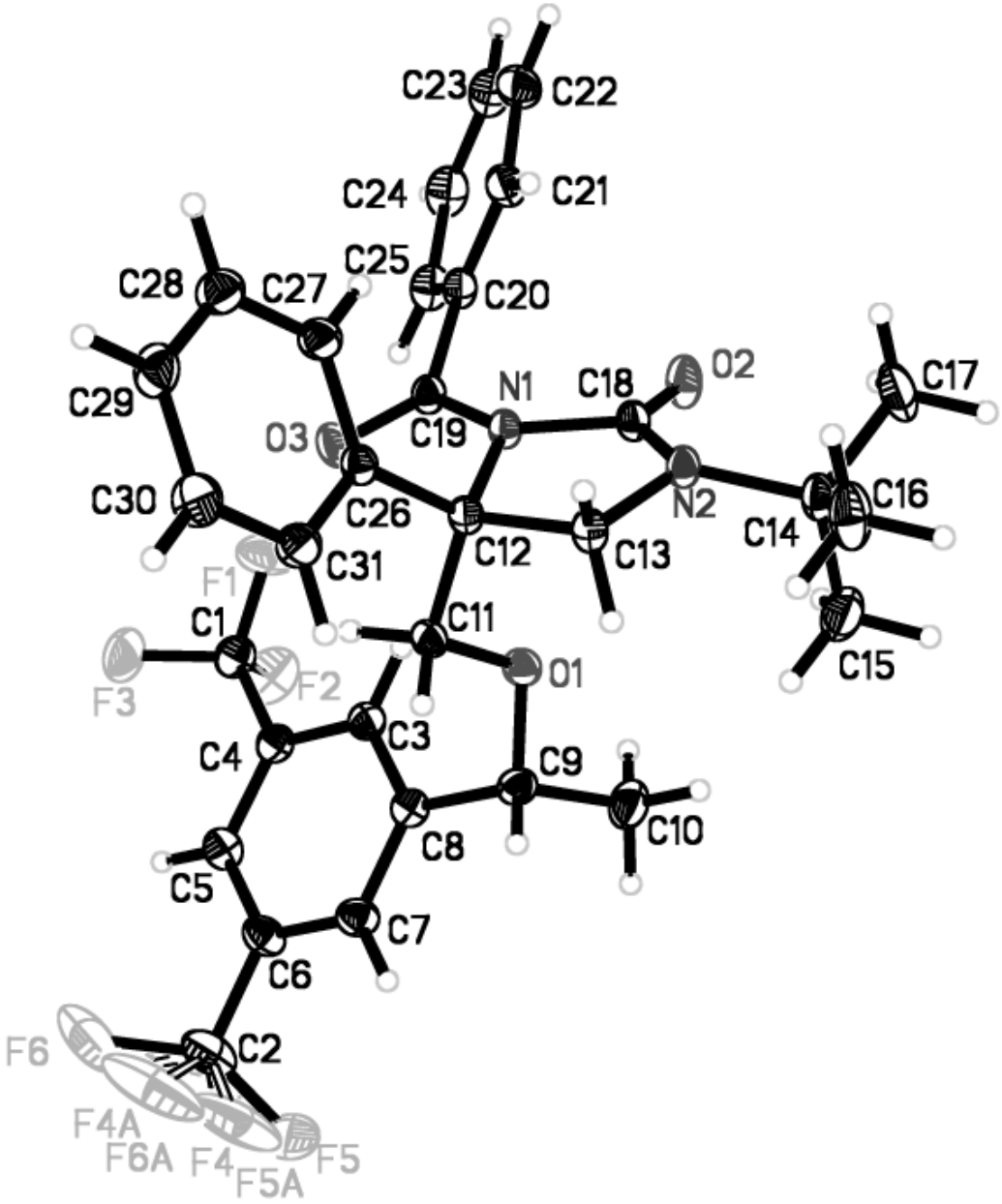


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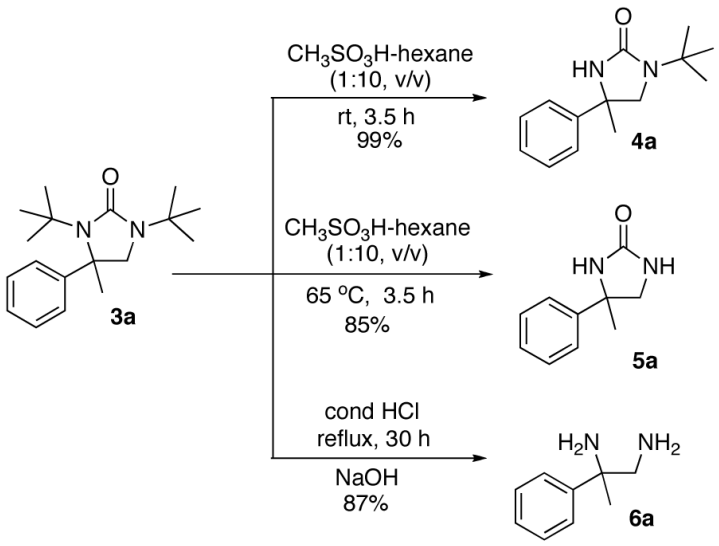
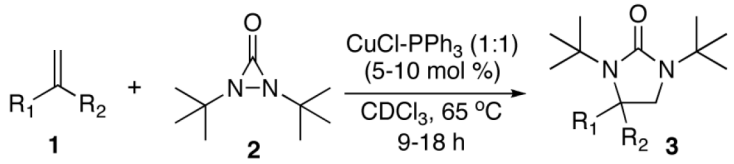


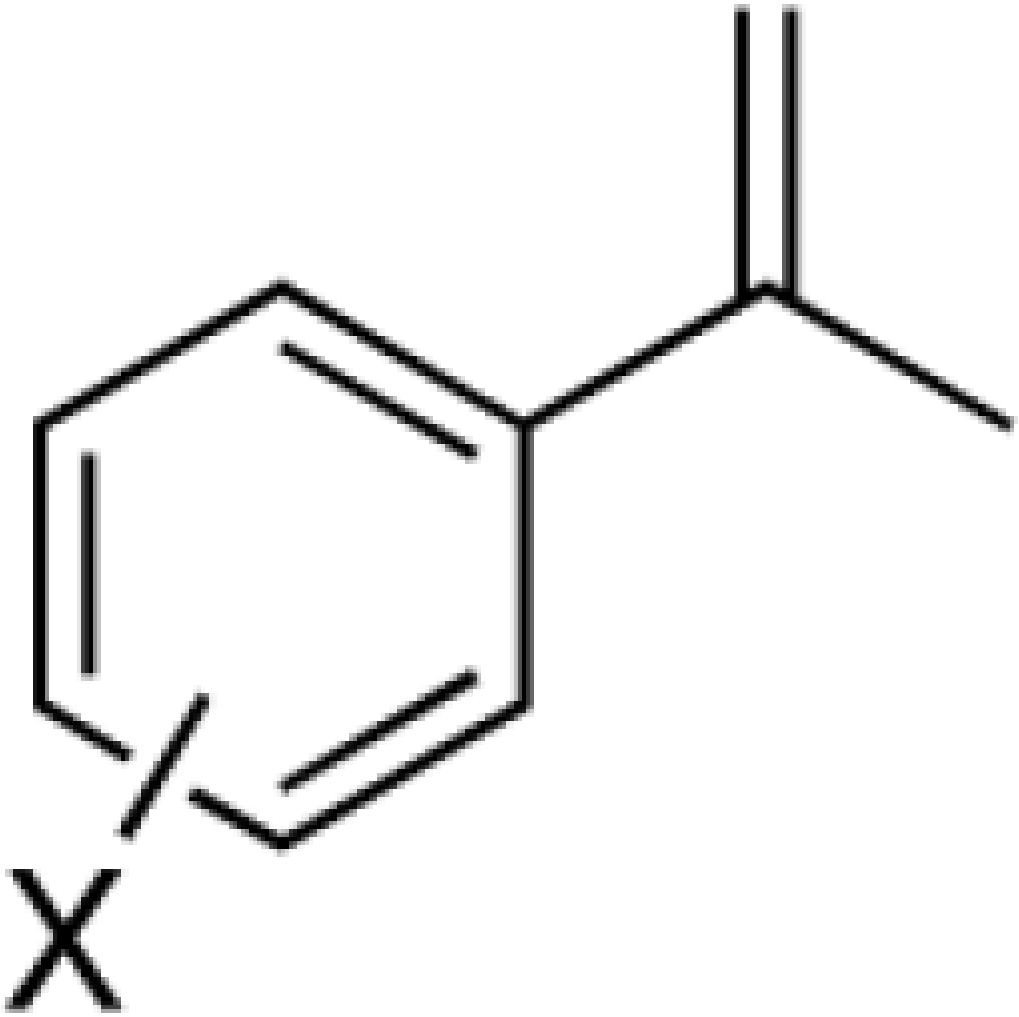

**Figure 2.**
The X-ray structure of compound **14.**

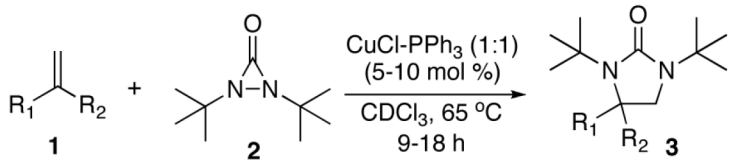
**Table 1**

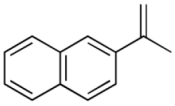
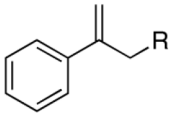
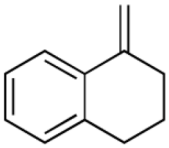
Catalytic Diamination of Disubstituted Terminal Olefins[a]

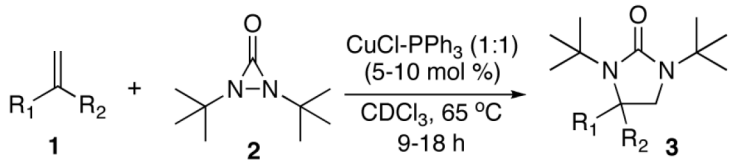


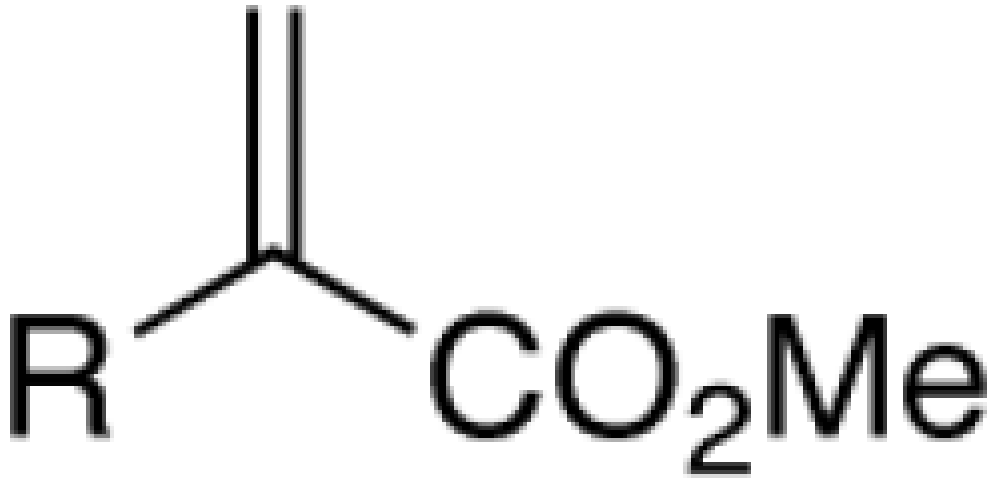

| entry | substrate 1 |
|---|---|
| 1 | **1a**, X = H |
| 2 | **1b**, X = *o*-F |
| 3[b] | **1c**, X = *o*-OMe |






| entry | substrate 1 |
|---|---|
| 4 | **1d**, X = *m*-Br |
| 5 | **1e**, X = *m*-OMe |
| 6 | **1f**, X = *m*-Me |
| 7 | **1g**, X = *m*-CN |
| 8 | **1h**, X = *p*-Me |
| 9 | **1i**, X = *p*- Cl |
| 10[c] |  **lj** |
| |  |
| 11 | **1k**, R = Me |
| 12 | **1l**, R = Ph |
| 13[b] | **1m**, R = OMe |
| 14 |  **ln** |




| entry | substrate 1 |
|---|---|
| 15 |  **1o**, R = Ph |
| 16 | **1p**, R = Me |

[a] All reactions were carried out with olefin (**1**) (0.4 mmol), di-*tert*-butyldiaziridinone (**2**) (0.8 mmol) (added by syringe pump over 8 h), CuCl-PPh3 (1:1) (0.02 mmol) in CDCl3 (0.3 mL) at 65 °C unless otherwise stated. Upon complete addition of **2**, the reaction mixture was stirred at 65 °C for an additional time period (1 h for entries 1, 4, 5, 6, 8, and 9; 2 h for entries 7, 10, and 15; 4 h for entry 11; 7 h for entries 3, 12, 14, and 16; 10 h for entries 2 and 13).

[b] CuCl-PPh3 (1:1) (0.04 mmol) was used.

[c] The reaction was carried out with olefin (0.2 mmol), di-*tert*-butyldiaziridinone (**2**) (0.4 mmol), and CuCl-PPh3 (1:1) (0.02 mmol) in CDCl3 (0.3 mL).

[d] Isolated yield based on olefin.