

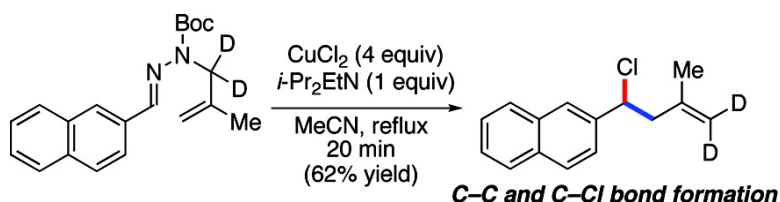
Communication

Tandem Carbon–Carbon and Carbon–Chlorine Bond Formation by Cu(II) Chloride-Promoted [3,3] Sigmatropic Rearrangement of *N*-Allylhydrazones

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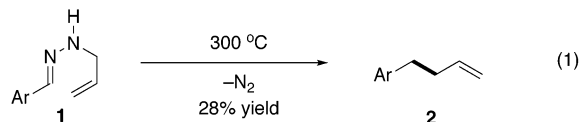
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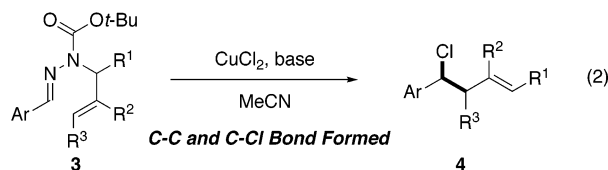
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The Wolff–Kishner reduction, in which a carbonyl function is converted to the corresponding methylene upon exposure to hydrazine and strong base, is arguably the most well-known hydrazone-based transformation.¹ This reaction involves the formation of carbon–hydrogen bonds, while other hydrazone transformations, such as hydrazone-based alkylations² afford carbon–carbon bond formation. *N*-Sulfonylhydrazones have been utilized for both carbon–hydrogen³ and carbon–carbon⁴ bond formation. A less familiar reaction is the thermal [3,3] sigmatropic rearrangement of *N*-allylhydrazones, which was reported by Stevens in 1973 (eq 1).⁵ As part of a research program aimed at exploiting the synthetic potential of *N*-allylhydrazones, we prepared a number of Boc-protected hydrazones (i.e., **3**) and now report a new Cu(II) chloride-promoted tandem carbon–carbon and carbon–chlorine bond forming reaction (eq 2).

Stevens (1973):

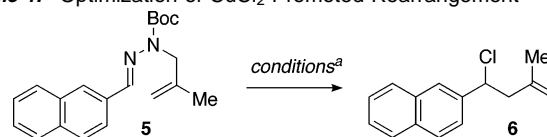


This work:



Our initial goal was to determine the effect that placing an electron-withdrawing substituent on the allyl-bearing nitrogen atom would have on the barrier to the thermal rearrangement of these hydrazones. Therefore, we prepared hydrazone **5** by simple condensation between 2-naphthaldehyde and the corresponding hydrazide, prepared according to the procedure described by Jamart-Grégoire and workers.⁶ Heating of **5** in toluene at reflux afforded no reaction (Table 1, entry 1), and while elevating the temperature may have resulted in some rearrangement we elected to explore the use of Lewis acids. In particular, we reasoned that azaphilic copper salts would be effective. However, under the assumed Lewis acidic conditions we did not expect loss of the Boc group or nitrogen extrusion to occur, and therefore treated **5** with one equivalent of CuCl₂ to ensure that turnover would not be an issue (Table 1, entries 2–6).⁷ To our surprise, the reactions conducted in dichloromethane and acetonitrile afforded the unexpected product **6** at approximately 25% conversion after 24 h at room temperature.⁸ Both a carbon–carbon bond and a carbon–chlorine bond are formed in this previously unknown rearrangement.⁹ The use of four equivalents of CuCl₂ in acetonitrile provided **6** with complete consumption of all starting material after 16 h (Table 1, entry 7).

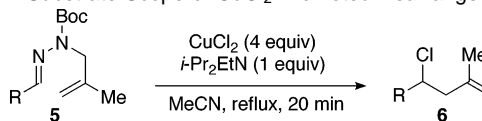
Table 1. Optimization of CuCl₂-Promoted Rearrangement



entry	solvent	temp (°C)	CuCl ₂ (equiv)	time (h)	conversion (%) ^b
1	toluene	110	0	24	0
2	toluene	23	1.0	24	0
3	THF	23	1.0	24	0
4	MeOH	23	1.0	24	0
5	DCM	23	1.0	24	25
6	MeCN	23	1.0	24	28
7	MeCN	23	4.0	16	100
8^c	MeCN	82	4.0	0.3	100

^a With 0.5 mmol **5**. ^b Determined by ¹H NMR spectroscopy. ^c Conducted in the presence of 1.0 equiv of diisopropylethylamine.

Table 2. Substrate Scope of CuCl₂-Promoted Rearrangement^a



entry	R	yield 6 (%) ^b
1	2-naphthyl (5a)	73 (6a)
2	1-naphthyl (5b)	55 (6b)
3	4-F-Ph (5c)	72 (6c)
4	4-Cl-Ph (5d)	58 (6d)
5	4-Br-Ph (5e)	62 (6e)
6	3-Cl-Ph (5f)	50 (6f)
7	2-Cl-Ph (5g)	26 (6g)
8	3,4-diCl-Ph (5h)	44 (6h)
9	Ph (5i)	56 (6i)
10	4-Me-Ph (5j)	48 (6j)
11	3-Me-Ph (5k)	45 (6k)
12	2-Me-Ph (5l)	44 (6l)
13	3-OMe-Ph (5m)	47 (6m)

^a With 1 mmol **5**. ^b Isolated yield after chromatography.

Heating the mixture to reflux decreased the reaction time to 20 min, but gave more complex mixtures. Because loss of the Boc-group presumably forms isobutene and an equivalent of acid, we surveyed a number of amine additives, and found the addition of one equivalent of diisopropylethylamine was effective at suppressing undesired byproducts (Table 1, entry 8). With optimized conditions developed (4 equiv of CuCl₂, 1 equiv of *i*-Pr₂EtN in acetonitrile at reflux for 20 min), we next examined the scope of this new transformation (Table 2).

Chloride **6a** could be reliably obtained from **5a** in an isolated yield of 73% (Table 2, entry 1). We found that electron-deficient aryl hydrazones provided higher yields of the desired chloride than electron-rich compounds. Halogen substitution at the 4-position

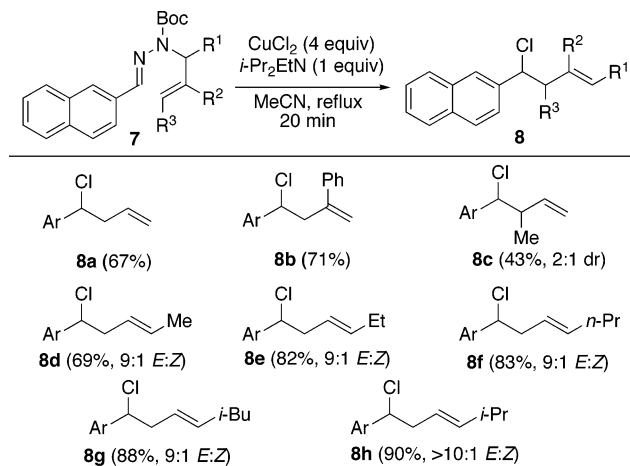
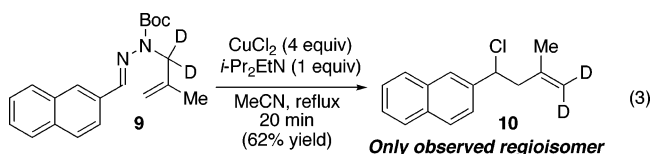


Figure 1. Variation of the hydrazide fragment, isolated yields. *E:Z* ratios determined by ^1H NMR spectroscopy.

afforded the corresponding benzyl chlorides in good yield (Table 2, entries 3–5), while 3-chloro and 2-chloro derivatives were slightly less effective (Table 2, entries 6 and 7). Phenyl hydrazone **5i** provided a 56% yield of **6i** (Table 2, entry 9). Methyl-substituted derivatives gave modest yields (Table 2, entries 10–12), while only 3-methoxy derivative **5m** provided the desired product when methoxy-substituted hydrazones were explored. The lower yields for these electron-rich systems is most likely a consequence of product instability. Aliphatic hydrazones gave complex reaction mixtures, and no chloride could be isolated.

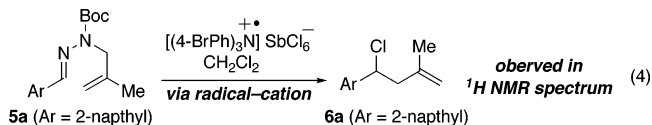
Several different hydrazine derivatives were prepared using the Jamart–Grégoire conditions⁶ and condensed with 2-naphthaldehyde to afford the corresponding hydrazones (i.e., **7**) in excellent yield. Exposure of these substrates to the optimized reaction conditions gave rise to the corresponding naphthyl chlorides (Figure 1). The simple allyl derivative **7a** gave chloride **8a** in 67% yield. Terminal substitution was tolerated, with crotyl-derived hydrazone **7c** providing the rearranged product **8c** as a single regioisomer (2:1 dr). This result provided initial evidence that the key carbon–carbon bond was generated through a [3,3] sigmatropic rearrangement. Further support for this hypothesis was gained when hydrazone **7d** produced only regioisomer **8d** in a 9:1 ratio of *E:Z* isomers. This regio- and stereoselectivity proved to be general for a number of additional substrates, providing a unique method for preparing stereodefined disubstituted olefins. Small quantities (~5%) of the corresponding diene products were also observed, but no attempt was made to optimize for these products.

Further evidence in favor of a concerted mechanism over a possible ionization–recombination mechanism was obtained when exposure of **9**¹⁰ to our standard conditions for chlorination provided regioisomer **10**, with no detectable traces of isotopic scrambling (eq 3). This result, in conjunction with the previously discussed syntheses of **8c–h**, is consistent with the hypothesis that the carbon–carbon bond is formed through a concerted intramolecular rearrangement.¹¹



We also investigated the ability of other metal salts to promote the rearrangement. Lewis acids such as ZnCl_2 , MgCl_2 , AlCl_3 , and TiCl_4 did not provide any of the corresponding chlorinated product.

We began to speculate that this new reaction might proceed by initial oxidation of the hydrazone to a radical–cation.¹² To test this notion we treated hydrazone **5a** with one equivalent of $(4\text{-BrPh})_3\text{N}^+\cdot\text{SbCl}_6^-$, a stable aminium salt known to promote radical–cation mediated reactions (eq 4).¹³ Although this transformation was not efficient, chloride **6a** was clearly observable in the ^1H NMR spectrum of the reaction mixture, providing initial evidence that these reactions may proceed via radical–cation intermediates.



In summary, we have discovered a new CuCl_2 -promoted [3,3] sigmatropic rearrangement of *N*-allylhydrazones that forms both a carbon–carbon and carbon–chlorine bond. Continuing research is focused on determining the mechanism of this new transformation, especially the activation and chlorination steps.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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