

Copper(I)-Catalyzed Addition of Grignard Reagents to in Situ-Derived *N*-Sulfonyl Azoalkenes: An Umpolung Alkylation Procedure Applicable to the Formation of Up to Three Contiguous Quaternary Centers

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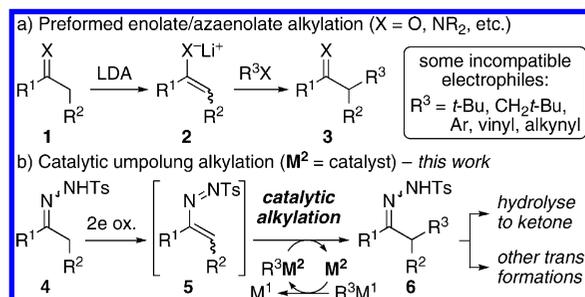
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Ketone α -alkylation is fundamental to organic synthesis. Notwithstanding the structural limitations of the electrophile, it is most often achieved by the addition of an alkyl halide to a preformed enolate/azaenolate (Scheme 1a). Transition metals have been investigated recently for catalytic ketone α -alkylation using a variety of enolate species or precursors.¹ Despite the impressive advances resulting from this work, a general catalytic alkylation method remains elusive. Umpolung alkylation, wherein an organometallic species adds to an electrophilic α -carbon provides an attractive alternative to enolate-based methods.² This strategy is well-suited to catalysis and also should prove to be general given the wide range of structures available as organometallic reagents (e.g., 1°, 2°, and 3° alkyl, aryl, vinyl, alkynyl). Herein, we describe the first Cu(I)-catalyzed addition of Grignard reagents to in situ-derived *N*-sulfonyl azoalkenes. This method is remarkable in its ability to deliver highly sterically hindered compounds that would be difficult or impossible to synthesize via traditional enolate chemistry, including those having up to three contiguous quaternary centers.

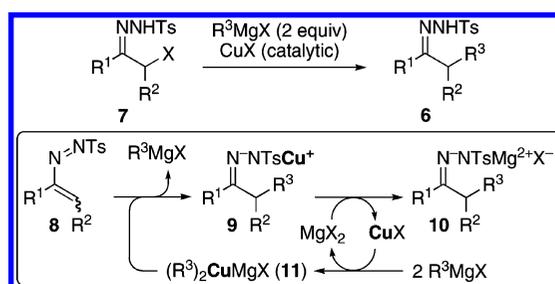
Our efforts were inspired by the realization that *N*-sulfonyl hydrazones offer a convenient entry point to umpolung alkylation (Scheme 1b). A two-electron oxidation would lead to an azoalkene intermediate (**4** \rightarrow **5**) that is susceptible to conjugate addition³ (**5** \rightarrow **6**) at the original α -carbon. Because of the highly reactive nature of azoalkenes, a stepwise alkylation procedure requiring their isolation is impractical. We reasoned, however, that if in situ azoalkene formation could be rendered compatible with a catalytic cycle leading to the production of a nucleophile capable of conjugate addition (cf. **5** \rightarrow **6**), then a general catalytic α -alkylation method should be attainable. Fuchs has shown that treatment of α -halo-*N*-sulfonyl hydrazones with 2.5 to 3 equiv of phenylcuprate leads to the formation of the corresponding azoalkenes, which undergo conjugate addition to provide the α -phenylated derivatives.^{3,4} On this basis, we anticipated the development of a Cu(I)-catalyzed addition of Grignard reagents to in situ-derived *N*-sulfonyl azoalkenes, as outlined in Scheme 2. An α -halo-*N*-sulfonyl hydrazone (**7**) would be combined with at least 2 equiv of a Grignard reagent and a catalytic amount of a Cu(I) salt. The Grignard reagent would both act as a Brønsted base to generate the azoalkene (**7** \rightarrow **8**) and undergo in situ transmetalation with the Cu(I) catalyst to form a cuprate (**11**)⁵ capable of conjugate addition to **8**. Transmetalation of the product (**9**) with MgX_2 would liberate the catalyst and **10**, the latter providing the α -alkylated product (**6**) on workup.

We began our study by attempting the ethylation of α -chloro-*N*-sulfonyl hydrazone **12** with EtMgBr (Scheme 3) and catalytic amounts of various Cu(I) salts.⁶ Gratifyingly, the reaction proceeded very well with a range of Cu(I) salts⁷ at catalyst loadings as low as 2 mol %. However, somewhat better results were obtained when 10 mol % CuCl was used, so these conditions were employed for the remainder of our studies.

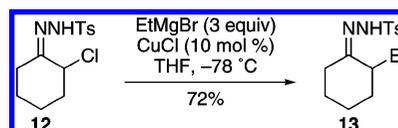
Scheme 1. Selected Approaches to α -Alkylation



Scheme 2. Proposed Cu(I)-Catalyzed Grignard Addition to in Situ-Derived *N*-Sulfonyl Azoalkenes

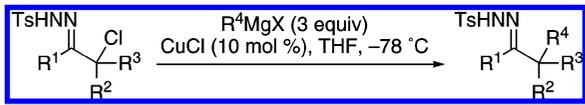


Scheme 3. CuCl-Catalyzed Ethylation of **12**

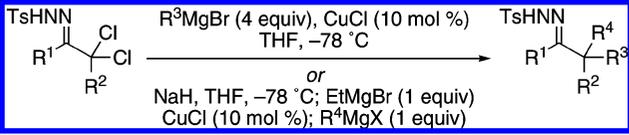


With suitable alkylation conditions available, we examined the scope of the transformation (Table 1). Primary, secondary, and tertiary Grignard reagents smoothly underwent the desired transformation with several different primary, secondary, and tertiary α -chloro-*N*-sulfonyl hydrazones derived from both ketones and aldehydes. Of particular note is the transformation in entry 18, in which compound **35** having two contiguous quaternary carbon centers was produced in 64% yield.

We next investigated the possibility of conducting one-pot α , α -bisalkylations beginning from α , α -dichloro-*N*-sulfonyl hydrazones. The success of these transformations would require that the sequential elimination of chloride and addition of the cuprate to the resulting azoalkene (cf. **7** \rightarrow **8** \rightarrow **9**, Scheme 2) occur twice in a cascading fashion. Our results are summarized in Table 2. Treatment of different α , α -dichloro-*N*-sulfonyl hydrazones with a Grignard reagent and CuCl catalyst indeed resulted in the incorporation of two identical alkyl groups (entries 1–6) in very good yield, considering that two alkylations had occurred. An especially impressive transformation is seen in entry 6, in which a bisalkylated

Table 1. Scope of the Cu(I)-Catalyzed Grignard Addition Reaction


entry	hydrazone	R ⁴	X	alkylated hydrazone	yield (%)
1	12	Et	Br	13	72
2	12	<i>i</i> -Pr	Br	19	60
3	12	<i>t</i> -Bu	Cl	20	66
4	14	Et	Br	21	70
5	14	<i>i</i> -Pr	Br	22	60
6	14	<i>t</i> -Bu	Cl	23	60
7	15	Et	Br	24	84
8	15	<i>i</i> -Pr	Br	25	72
9	15	<i>t</i> -Bu	Cl	26	67
10	16	Et	Br	27	67
11	16	<i>i</i> -Pr	Br	28	68
12	16	<i>t</i> -Bu	Cl	29	64
13	17	Et	Br	30	72
14	17	<i>i</i> -Pr	Br	31	68
15	17	<i>t</i> -Bu	Cl	32	64
16	18	Et	Br	33	86
17	18	<i>i</i> -Pr	Br	34	77
18	18	<i>t</i> -Bu	Cl	35	64
19	18	Bn	Br	36	50
20	18	CH ₂ <i>t</i> -Bu	Br	37	49
21	18	Ph	Br	38	64

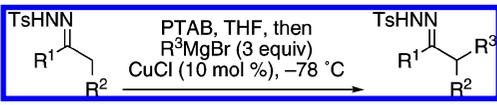
Table 2. α,α -Bisalkylation of α,α -Dichloro-*N*-sulfonyl Hydrazones


entry	R ¹	R ²	R ³	R ⁴	X	yield (%)
1 ^a	Me	Me	Et	Et	Br	68
2 ^a	Me	Me	<i>i</i> -Pr	<i>i</i> -Pr	Br	62
3 ^a	Me	Me	<i>t</i> -Bu	<i>t</i> -Bu	Cl	48
4 ^a	H	Et	Et	Et	Br	64
5 ^a	H	Et	<i>i</i> -Pr	<i>i</i> -Pr	Br	62
6 ^a	H	Et	<i>t</i> -Bu	<i>t</i> -Bu	Cl	58
7 ^b	Me	Me	Et	<i>i</i> -Pr	Br	58
8 ^b	Me	Me	Et	<i>t</i> -Bu	Cl	56
9 ^b	Me	Me	Et	CH ₂ <i>t</i> -Bu	Br	52
10 ^b	H	Et	Et	<i>i</i> -Pr	Br	58
11 ^b	H	Et	Et	<i>t</i> -Bu	Cl	56
12 ^b	H	Et	Et	CH ₂ <i>t</i> -Bu	Br	52

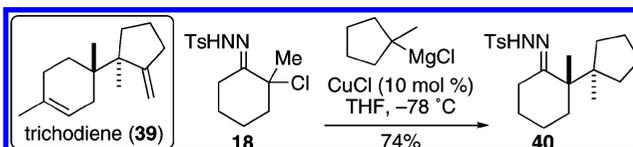
^a R³MgBr (4 equiv), CuCl (10 mol %), THF, -78 °C. ^b NaH, THF, -78 °C; EtMgBr (1 equiv), CuCl (10 mol %); R⁴MgX (1 equiv).

product having *three contiguous quaternary centers* was produced in 58% yield. We next attempted the bisalkylation using two different Grignard reagents (entries 7–12). To do so, the initial azoalkene was generated using NaH and then treated with the first Grignard reagent and copper catalyst. After 1.5 h, the second Grignard reagent was added. In each case, the desired bisalkylated compound having two different alkyl groups was generated.

To investigate the possibility of coupling hydrazone oxidation with the catalytic alkylation reaction, *N*-sulfonyl hydrazones were treated with phenyltrimethylammonium tribromide (PTAB) to generate the α -bromo-*N*-sulfonyl hydrazones⁸ and then exposed to the catalytic alkylation conditions (Table 3). We were pleased to find that in every case the desired α -alkylated product was produced from this sequential transformation.

Table 3. Sequential Oxidation/Alkylation of *N*-Sulfonyl Hydrazones


entry	R ¹	R ²	R ³	yield (%)
1	—CH ₂ CH ₂ CH ₂ CH ₂ —	—	Et	63
2	—CH ₂ CH ₂ CH ₂ CH ₂ —	—	<i>i</i> -Pr	60
3	—CH ₂ CH ₂ CH ₂ CH ₂ —	—	<i>t</i> -Bu	52
4	Ph	H	Et	74
5	Ph	H	<i>i</i> -Pr	68
6	Ph	H	<i>t</i> -Bu	58

Scheme 4. Concise Synthesis of the Trichodiene Core

Finally, the synthetic potential of this catalytic alkylation method was tested by carrying out a concise synthesis of the core framework of the natural product trichodiene (**39**, Scheme 4).⁹ To do so, **18** was treated with 1-methylcyclopentylmagnesium chloride to produce **40** in 74% yield, enabling the direct linkage of the adjacent quaternary carbon centers in a single step.

In conclusion, we have developed the first Cu(I)-catalyzed addition of Grignard reagents to in situ-derived *N*-sulfonyl azoalkenes. This umpolung alkylation reaction enables the synthesis of extremely hindered compounds that would be inaccessible using traditional enolate chemistry and also provides a unique approach to regiocontrolled α,α -bisalkylation. Studies of the development of an asymmetric version of this transformation are underway.

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

References

- (1) For example, see: (a) Berger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 2603. (b) Berger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (c) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (d) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62. (e) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (f) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192. (g) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718. (h) Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720.
- (2) For ketones, see: Lundin, P. M.; Esquivias, J.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 154. Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240. For carboxylate derivatives, see: Brand, G. J.; Studte, C.; Breit, B. *Org. Lett.* **2009**, *11*, 4668. Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451. Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302. Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.
- (3) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372.
- (4) Fuchs has also shown that Me₂CuLi and *t*-Bu₂CuLi add to preformed tosylazocyclohex-1-ene to give α -methyl- and α -*t*-Bu-tosylcyclohexanone, respectively (see ref 3).
- (5) Lipshutz, B. H. In *Organometallics in Synthesis*, 1st ed.; Schlosser, M., Ed.; Wiley: Chichester, U.K., 1994; p 339.
- (6) See the Supporting Information for details.
- (7) The use of EtMgBr alone did not lead to product formation.
- (8) Rosini, G.; Baccolini, G. *J. Org. Chem.* **1974**, *39*, 826.
- (9) Schlessinger, R. H.; Schultz, J. A. *J. Org. Chem.* **1983**, *48*, 407. Snowden, R. L.; Brauchli, R.; Sonnay, P. *Helv. Chim. Acta* **1989**, *72*, 570. (b) Tanaka, M.; Sakai, K. *Tetrahedron Lett.* **1991**, *32*, 5581. (c) Kitano, Y.; Fukuda, J.; Chiba, K.; Tada, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 829. (d) Lange, G. L.; Furlan, L.; MacKinnon, M. C. *Tetrahedron Lett.* **1998**, *39*, 5489.

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