JOC Article

Alkenenitriles: Conjugate Additions of Alkyl Iodides with a Silica-Supported Zinc−Copper Matrix in Water

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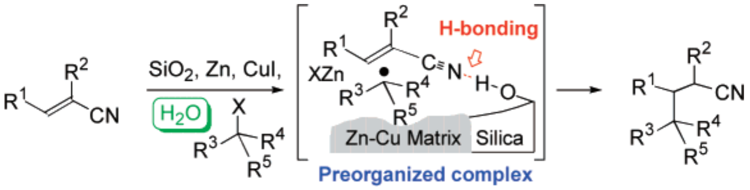

A new silica-supported zinc-copper matrix reagent promotes the conjugate addition of alkyl iodides to cyclic and acyclic alkenenitriles in water. X-ray diffraction and electron microscopy techniques suggest that the active copper species generated from elemental zinc and copper(I) iodide is finely dispersed, zerovalent copper. Alkyl iodides react with the silica-supported reagent to generate putative radicaloid intermediates that efficiently add to alkenenitriles to provide β-substituted nitriles. Conjugate additions to acyclic and cyclic 5−7-membered alkenenitriles are most effective for primary alkyliodides, although secondary and tertiary alkyliodides are viable reaction partners. The strategy addresses the challenge of performing conjugate additions to disubstituted alkenenitriles and demonstrates the beneficial role of the silica-supported reagent.

Introduction

Conjugate addition reactions rank among the most important carbon−carbon bond-forming reactions in organic synthesis.[1] The centrality of conjugate addition reactions stems from the efficient, stereoselective, installation of a new bond two or more carbons removed from an electron-withdrawing group, with the potential for subsequent α-alkylation.[2] A measure of the maturity of this transformation is gained from the diversity of organometallic reagents capable of delivering carbon nucleophiles to cyclic and acyclic electron-deficient alkenes.[3]

Despite dramatic advances in organometallic additions to unsaturated carbonyl derivatives, the analogous conjugate additions to alkenenitriles remain notoriously difficult.[4] The paucity of conjugate additions to alkenenitriles stems in part from the powerful inductive effect of the electron-withdrawing nitrile group that polarizes the adjacent α-carbon of the alkene more than the β-carbon.[5] Comparable carbonyl systems are polarized by resonance effects which are accentuated by metal complexation to the carbonyl oxygen.[6] Nitriles, in contrast, are relatively poor Lewis bases and are not readily activated by Lewis acidic metal cations.[7] Consequently, organometallic reagents tuned for conjugate additions to unsaturated carbonyl compounds are often relatively poor reagents for analogous additions to alkenenitriles. For example, several organocopper[8] and phenolic[9] nucleophiles simply do not react with many alkenenitriles, whereas more nucleophilic reagents preferentially add to the nitrile group.[10]

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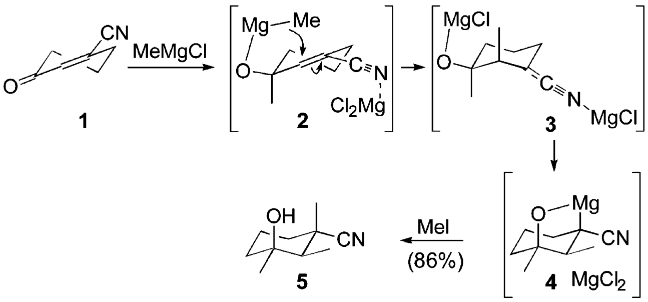
Grignard reagents are sufficiently nucleophilic to overcome the recalcitrance of alkenenitriles toward conjugate addition provided that two aryl substituents are present on the α- and *β*-carbons.[4] Other highly nucleophilic organometallics engage in conjugate additions to cyclic alkenenitriles devoid of aromatic substituents in intramolecular additions provided that the geometry of the alkenenitrile precludes attack on the CN unit.[11] A related strategy is to temporarily tether nucleophilic organometallics adjacent to an alkenenitrile through an alkoxide generated by addition to a ketone[12] or deprotonation of an alcohol.[13] For example, addition of a Grignard reagent to oxonitrile **1**[14] generates a halomagnesium alkoxide, through carbonyl addition, which triggers a halogen−alkyl exchange[15] with a second Grignard to afford the alkyl magnesium alkoxide **2** (Scheme 1). Subsequent conjugate addition leads to the bis-magnesiated nitrile **3** that rearranges to the *C*-magnesiated nitrile **4**. Intercepting **4** with electrophiles allows a formal intermolecular conjugate addition−alkylation through the entropically more favorable[16] intramolecular delivery of the carbon nucleophile.

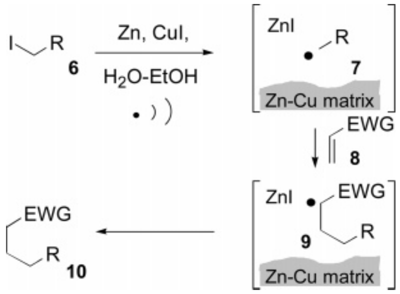
SCHEME 1. Chelation-Controlled Conjugate Addition to a Cyclic Alkenenitrile



Intermolecular conjugate additions of organometallic reagents to cyclic alkenenitriles remain a significant challenge. A few organometallic reagents permit conjugate additions to acrylonitrile, the most reactive alkenenitrile, although most organometallic reagents are unable to react with substituted acrylonitriles.[4] Presumably the combination of increased steric demand and diminished electrophilicity prevents the conjugate addition, explaining why very few methods are effective with cyclic alkenenitriles which necessarily contain two substituents as part of the ring.[17]

Historically, the reagent combination of elemental zinc, copper(I) iodide, and an alkyliodide[18] provided a seminal advance in conjugate additions to alkenenitriles.[19] Intensive optimization in related conjugate additions with enones identified two critical reaction parameters: the use of a mixed alcohol−water solvent combination, and ultrasonic irradiation (Scheme 2).[20] Under optimal conditions, alkyl iodides and bromides engage in conjugate addition reactions with monosubstituted enoates, enamides, and alkenenitriles. Although the precise mechanistic details remain uncertain, several key features point to radical or radicaloid intermediates.[21] An electron transfer at the metal−iodide interface is thought to reduce the alkyl iodide **6**, possibly by electron transfer, to a surface-adsorbed radical **7** (Scheme 2).[19a] Subsequent radical addition to an electron-deficient olefin **8**, such as acrylonitrile, generates a stabilized radical **9** that is reduced and protonated to afford the conjugate addition product **10**.

SCHEME 2. Zn−CuI Conjugate Addition to Activated Alkenes



The exceptional ability of the zinc−copper alkyliodide reagent to trigger conjugate additions of alkyl iodides to acyclic alkenenitriles provided an excellent lead for the more challenging conjugate additions to cyclic alkenenitriles. Extensive optimization experiments have identified conditions for this transformation and stimulated a series of material analyses that provide new insight into the nature of the active species previously referred to as a zinc−copper couple. Collectively, this methodology addresses the long-standing difficulty of conjugate additions to disubstituted alkenenitriles, demonstrates the dramatic influence of performing the reaction in the presence of silica gel, and provides key insight into the exact nature of the reagent generated from elemental zinc and copper(I) iodide.

Results and Discussion

Lead optimization forays engaged 1-chloro-4-iodobutane in a conjugate addition with cyclohexenecarbonitrile (**11a**). The

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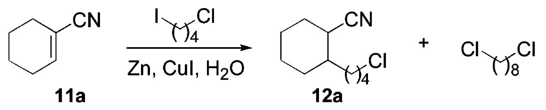
(21) Several cleverly designed conjugate additions to enones have trapped the presumed intermediates by employing internal radical traps. The yields of trapped product are typically in the range of 5−10% and in some cases the radical is unable to be intercepted: (a) Sarandeses, L. A.; Mourino, A.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1992**, 798. (b) Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373.

attraction of **11a** as a prototype lies in the potential for subsequent cyclization of the product **12a** (eq 1).[22]



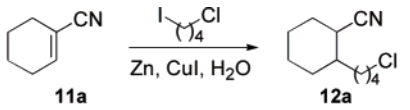
(1)

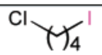
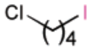
Under standard conditions,[18] with elemental zinc and copper(I) idodide, only a trace of the desired conjugate addition product **12a** is observed. An intensive screening of solvent identified pure water at ambient temperature as the best medium with mixed organic−water combinations being significantly less effective.[23] Performing the reaction neat with grinding accelerated the reaction but with poor mass recovery, presumably as a result of alkenenitrile polymerization.[24] Varying the reaction temperature exerted a deleterious effect: higher temperatures accelerate the reaction but lead to poor mass recovery, whereas lowering the temperature to 0 °C causes the reaction to stall. Ultrasonic irradiation,[25] the use of copper alloys, different copper(I) and -(II) salts,[26] surfactants,[27] Lewis acids,[27a] and metal additives[28] were similarly deleterious.

Closely monitoring the reaction revealed the rapid formation of 1,8-dichlorooctane, presumably by radical dimerization. Slow syringe pump delivery of the alkyliodide was probed as a means of enhancing the lifetime of the surface generated radical, although this proved less effective than the portion-wise addition at varying time intervals. Eventually the most profitable procedure was to simply add the alkyl iodide at 1 h intervals, which provided the nitrile **12a** in 4% yield (Table 1, entry 1). After pursuing numerous addition combinations, a synthetically viable procedure was identified in which 1 equiv of the iodide was added every hour for 8 h (a total of 8 equiv including the initial addition) with two additional infusions of Zn and CuI added at 3 h intervals (Table 1, entry 2). Employing this addition procedure with the corresponding bromide provides nitrile **12a** in a slightly lower yield, which correlates with the increased bond strength of alkylbromides (Table 1, entry 3).

Further optimization focused on improving the poor mass recovery in these remarkably clean reactions. Suspecting that the diminished mass balance is due to radical polymerization, the finely dispersed zinc−copper matrix was absorbed onto silica gel prior to the introduction of nitrile **11a** and 1-chloro-4-iodobutane—the aim being to adsorb the radical onto a surface proximal to the alkenenitrile. Experimentally the addition of silica gel significantly increases the yield of the nitrile **12a** (Table 1, compare entries 2 and 5). Celite exhibits a similar beneficial effect although the use of silica gel and the more frequent addition of Zn, Cu(I)I, and silica gel affords the best yield (Table 1, compare entries 6 and 7). In each case, depositing the zinc−copper matrix onto silica gel or celite significantly enhances the mass recovery of the crude product, which essentially contains only **12a**, dichlorooctane, and unreacted 1-chloro-4-iodobutane.

TABLE 1. Optimizing Conjugate Additions to Cyclic Nitrile 11a



entry	alkyl halide (equivalents)	reagent (equivalents)	yield
1	 (3)	Zn-Cu[a]	4%
2	 (9)	Zn-Cu[b]	43%
3	 (9)	Zn-Cu[b]	33%
4	 (9)	SiO_2-Zn-Cu[d]	34%
5	 (9)	SiO_2-Zn-Cu[c]	64%
6	 (9)	Celite-Zn-Cu[d]	76%
7	 (9)	SiO_2-Zn-Cu[d]	86%

[a] Standard conditions for Zn−Cu promoted additions except with 3 equiv of iodide and using pure water as the solvent. [b] Using the general procedure without silica gel. [c] Using the general procedure with silica—see the Experimental Section. [d] Using the general procedure with Zn−CuI additions at 2, 4, 6, and 8 h intervals.

Comparative conjugate additions of alkylhalides to acyclic and cyclic 5- through 7-membered alkenenitriles are consistently more efficient with the silica-modified zinc−copper matrix than with the conventional reagent (Table 2, columns b and a, respectively.) Primary alkyliodides react selectively over alkylchlorides and fluorides, providing access to modestly functionalized, β-substituted, haloalkanenitriles (Table 2, entries 1−4 and 12−19). Although the efficiency with 1,3-dibromopropane is modest, the reaction is remarkable in installing a bromopropyl group without dimerization or reduction and protonation (Table 2, entry 12). The modest efficiency for the conjugate addition with isopropyl iodide is surprising, because the addition of structurally similar cyclohexyl iodide proceeds with the highest yield of any alkylhalide (Table 2, compare entries 5 and 6). The discrepancy may reflect solvation differences, because iodoalkanes bearing polar hydroxyl or carbomethoxy groups afford only traces of the conjugate addition products.

Insight into the nature of the radical intermediate was probed through conjugate additions to **11a** with bromomethylcyclopropane and iodoalkanes containing alkene and alkyne functional groups (Table 2, entries 9−11). Bromomethylcyclopropane (**13**) reacts with nitrile **11a** to afford alkenenitrile **12j**, the formal

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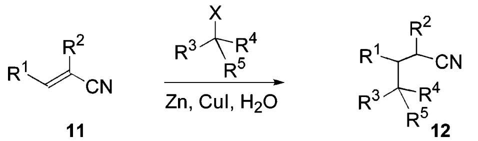
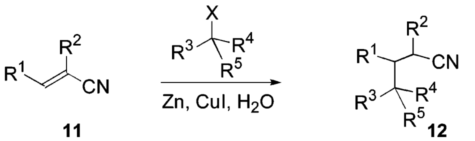
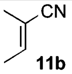
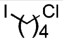
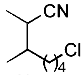
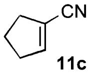
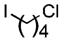
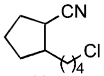
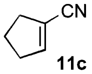
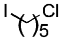
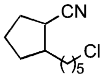
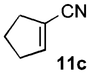
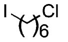
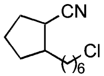
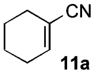
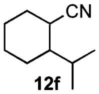
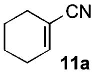
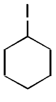
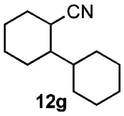
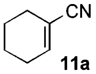
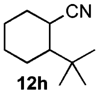
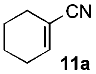
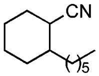
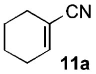
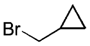
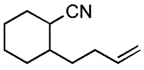
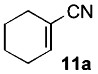
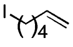
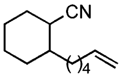
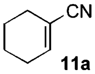
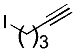
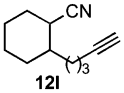
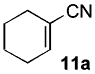
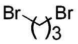
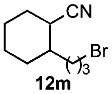
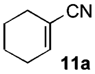
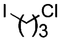
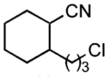
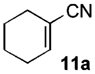
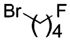
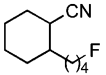
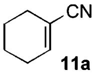
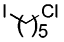
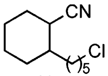
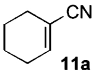
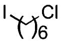
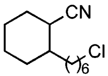
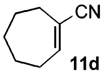
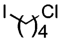
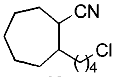
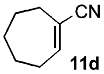
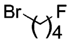
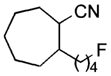
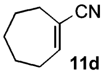
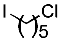
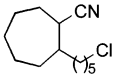
TABLE 2. Conjugate Addition of Alkylhalides to Alkenenitriles





entry	alkenenitrile	alkyl iodide	alkanenitrile	yield (%)[a] a	yield (%)[a] b
1	 **11b**		 **12b**	17	72
2	 **11c**		 **12c**	45	78[b]
3	 **11c**		 **12d**	36	82
4	 **11c**		 **12e**	31	74
5	 **11a**		 **12f**	32	13
6	 **11a**		 **12g**	50	94
7	 **11a**		 **12h**	27	14
8	 **11a**		 **12i**	58	63
9	 **11a**		 **12j**	19	-
10	 **11a**		 **12k**	-	80
11	 **11a**		 **12l**	38[c]	-
12	 **11a**		 **12m**		53[d]
13	 **11a**		 **12n**	45	35[e]
14	 **11a**		 **12o**	-	43
15	 **11a**		 **12p**	56	73
16	 **11a**		 **12q**	64	76
17	 **11d**		 **12r**	-	80[f]
18	 **11d**		 **12s**	-	43
19	 **11d**		 **12t**	-	71

[a] Column a: Zinc−copper matrix in water. Column b: Silica-supported zinc−copper matrix. [b] The yield with Celite−Zn−Cu is 77%. [c] Accompanied by 4% of the alkene derived by reduction of the triple bond. [d] Using the general procedure with Zn−CuI additions at 2, 4, 6, and 8 h intervals. [e] The yield with Celite−Zn−Cu is 39%. [f] The yield with Celite−Zn−Cu is 67%.

product of butenyl addition (Scheme 3). Forming the ring-opened product implies an initial reduction of cylcopropylmethylbromide to a cyclopropylmethyl-type radical **14** ($n = 1$) that rapidly fragments to the corresponding butenyl radical **15** ($n = 1$).[29] Subsequent addition of **15** ($n = 1$) to alkenenitrile **11a** affords the nitrile-stabilized radical **16** that is reduced and protonated to afford **12j**. The inability to detect any of the hydrindane **17** arising from intramolecular addition of the nitrile-stabilized radical onto the pendant alkene indicates that the lifetime of the intermediate is very short[30] or that interaction

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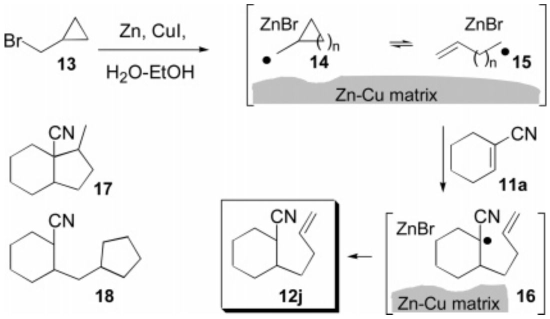
(29) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

SCHEME 3. Mechanistic Probes for the Zn−Cu(I) Conjugate Addition

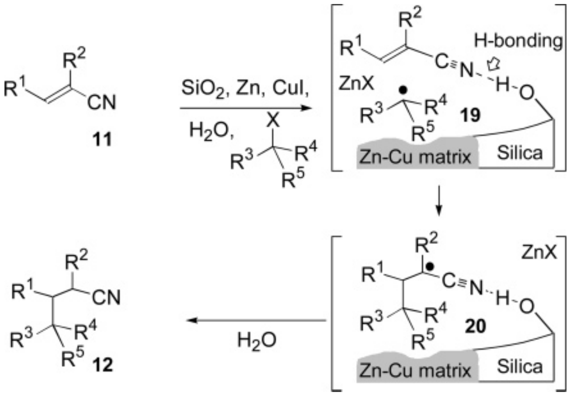


with the zinc−copper matrix generates a radicaloid with reactivity different from that of a free radical. Similarly, no bicyclic nitriles were detected during the conjugate addition of 5-iodopentyne to alkenenitrile **11a** (Table 2, entry 11) where cyclization of the nitrile-stabilized radical could occur onto the pendant alkyne. The inability to detect any hydrindane from this reaction is significant, because 4% of an alkenenitrile resulting from reduction of the triple bond was isolated from the reaction.

6-Iodohex-1-ene adds smoothly to **11a** to afford **12k** (Table 2, entry 10) without any cyclopentylmethyl addition that could potentially arise by cyclization of the first formed radical (Scheme 3, **15** ($n = 3$) → **14** ($n = 3$) → **18**).[31] Formation of radicaloid intermediates correlates with similar reactions that are inhibited with radical traps[20a] and in which stereochemical scrambling occurs with chiral secondary iodides.[19a] Radicaloid intermediates are further implied from conjugate additions with 1,3-dibromopropane and 1-chloro-3-iodopropane (Table 2, entries 12 and 13, respectively) where the formation of a true organometallic would lead to reagent annihilation through rapid cyclization to cyclopropane. Collectively, these mechanistic probes implicate radicaloid intermediates with reactivities similar to, but not identical with, those of the corresponding free radical.[32]

Mechanistically the conjugate additions with and without silica gel most plausibly occur by reduction of the alkyl halide to generate a surface-adsorbed radical or radicaloid (Scheme 4). The reduction is analogous to that proposed for related conjugate additions of alkylhalides to alkenenitriles with elemental zinc,[33] a zinc−$FeCl_3$ combination,[34] and a reagent system composed of catalytic $PbCl_2$ and elemental manganese.[35] Silica gel is particularly abrasive[36] and may facilitate maximum surface exposure by grinding the zinc−copper matrix. Although speculative, the silica gel might further function to provide a reactive metal surface in close proximity to an alkenenitrile anchored in position by hydrogen bonding to the nitrile nitrogen (**19**, Scheme 4).[37] In this scenario, the aqueous solvent favors localization of the two hydrophobic organic reagents at the metal surface.[38] Approach of the alkyliodide to the preorganized complex **19** generates a radicaloid species ideally positioned for addition to the adjacent alkenenitrile.

SCHEME 4. Silica-Supported Zn−CuI Conjugate Addition



Conversion of the resulting nitrile-stabilized radical **20** to the neutral nitrile requires either reduction and protonation, or hydrogen atom abstraction (Scheme 4). A one-electron reduction of the nitrile-stabilized radical can be envisaged to generate a zincated nitrile that will undergo protonation by the hydroxylic solvent.[39] An alternative process that might be considered is hydrogen atom abstraction from a zinc iodide−water complex since Lewis acid complexation of water by trialkylboranes sufficiently lowers the O−H bond energy for water to act as a hydrogen atom source in a related reduction.[40]

Materials Characterization. Complicating the mechanistic details is the elusive identification of the exact reagent generated from zinc dust and copper(I) iodide. Typically the resulting black suspension is loosely referred to as a zinc−copper couple.[41] Optimizing the ratio of zinc to copper(I) iodide demonstrates a very narrow effective ratio for generating an active, black reagent. The optimum ratio is 6 equiv of zinc to 1 equiv of Cu(I)I with other ratios resulting in a significant loss of activity or black materials devoid of any ability to react with alkyliodides.

Insight into the composition and morphological nature of the reagent was provided by a series of materials characterization analyses. Powder X-ray diffraction data (Figure 1) from samples of the zinc−copper matrix exhibit diffraction patterns readily indexed to three crystalline phases: $Zn(OH)_2$,[42] Zn metal,[43] and

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[30] Newcomb, M.; Horner, J. H.; Filipkowski, M. A.; Ha, C.; Park, S.-U. *J. Am. Chem. Soc.* **1995**, *117*, 3674.

[31] The related addition to ethyl vinyl sulfone affords a 2:1 ratio of cyclopentylmethyl and hexenyl addition: Zhao, M. M.; Qu, C.; Lynch, J. E. *J. Org. Chem.* **2005**, *70*, 6944.

[32] Related radical probes with enones and enoates similarly imply radicaloid intermediates and in one instance intramolecular cyclization onto a pendant alkyne occurs in 10% yield.[18]

[33] Yamamoto, Y.; Nakano, S.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2004**, *6*, 799.

[34] Blanchard, P.; Da Silva, A. D.; El, Kortbi, M. S.; Fourrey, J.-L.; Machado, A. S.; Robert-Gero, M. *J. Org. Chem.* **1993**, *58*, 6517.

[35] (a) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990. (b) Takai, K.; Ueda, T.; Ikeda, N.; Ishiyama, T.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 347.

[36] After the reaction the octagonal stir bar is noticeably concave as a result of the abrasive action of silica on the Teflon coating.

[37] Le Questel, J. Y.; Berthelot, M.; Laurence, C. *J. Phys. Org. Chem.* **2000**, *13*, 347.

[38] (a) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492. (b) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12*, 1313. (c) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275.

[39] Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990.

[40] Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513.

[41] Unpublished X-ray analysis of the material indicated that the material is not a copper hydride: ref 18, footnote 7.

[42] Stahl, R.; Jung, C.; Lutz, H. D.; Kockelmann, W.; Jacobs, H. *Z. Anorg. Allg. Chem.* **1998**, *624*, 1130.

[43] Swanson, H. E.; Tatge, E. *Natl. Bur. Stand. (U.S.) Circ.* **1953**, *359*, 539.

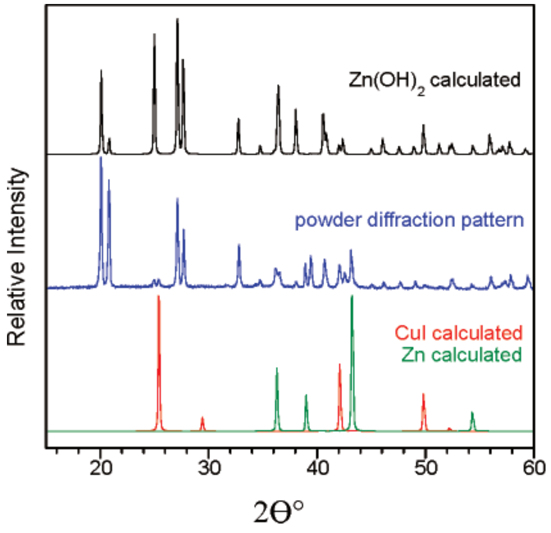

FIGURE 1. Powder X-ray diffraction patterns of the zinc−copper matrix compared to calculated patterns for $Zn(OH)_2$, Zn metal, and CuI.[45]

CuI.[44] Comparison of the intensities identifies the main component as $Zn(OH)_2$ accompanied by small amounts of residual zinc metal and CuI. Significantly, the powder X-ray diffraction pattern does not identify a major crystalline phase containing copper. Essentially the same powder diffraction pattern is obtained from the sample prepared in the presence of silica gel, accompanied by additional peaks from the silica support.

An energy dispersive spectrum (Figure 2) shows that the material consists of mainly zinc and copper with very little iodine. Semiquantitative energy dispersive analysis focusing on the zinc, copper, and iodine in these samples indicates the total elemental composition is approximately 78% zinc, 19% copper, and only 3% iodine (∼4:1 zinc to copper ratio). These data are also supported by ICP analysis of the material, which identifies zinc and copper in a ratio of approximately 5:1. Collectively these data support the presence of a major copper-containing component in the matrix that is not CuI. The inability to detect the major copper component by powder X-ray diffraction, combined with the EDS and ICP analyses, indicates that the copper is present either in a noncrystalline form or has a very small particle size, not readily detected in the presence of strongly diffracting phases such as $Zn(OH)_2$.

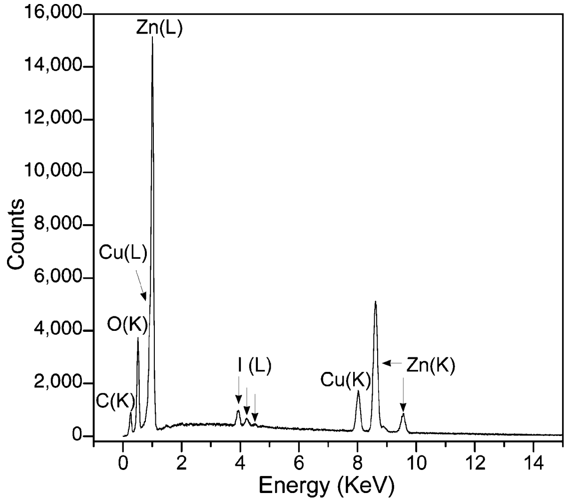

FIGURE 2. Energy dispersive spectrum of the zinc−copper matrix.[46]

Thermogravimetric analysis (TGA) provided some illumination into the nature of the elusive copper species. TGA analysis drives off any absorbed water and allows metal oxidation which, for the zinc−copper matrix in air, causes a 2.9% weight loss upon heating to 1200 °C. Powder X-ray diffraction analysis of the TGA residue provides an indirect, qualitative identification of the composition of zinc and copper in the original matrix. Diffraction peak indexing indicates the original material to be oxidized primarily to ZnO accompanied by a lesser, but significant quantity of CuO, and a very small amount of a brass, Cu_3Zn (Figure 3). Presumably heating the zinc−copper matrix in air causes dehydration of zinc hydroxide to zinc oxide and oxidation of the zerovalent copper species to copper oxide.

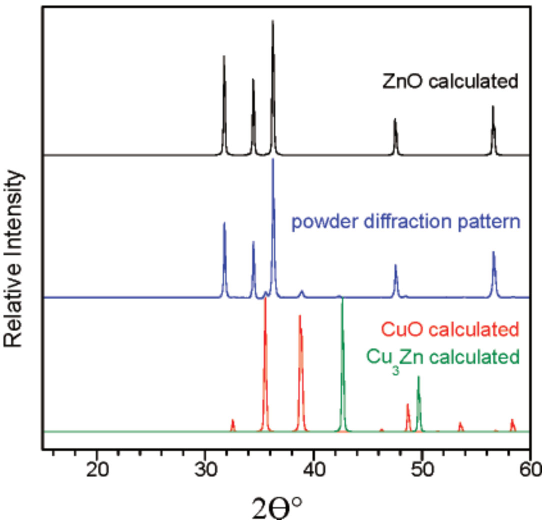

FIGURE 3. Powder X-ray diffraction pattern of the zinc−copper matrix after TGA.[47]

Further insight into the elemental composition and particle morphology was obtained from electron microscopy in combination with Energy Dispersive Spectroscopy (EDS) for identifying the composition of individual regions embedded within the matrix (Figure 4). Electron micrographs collected with a Field Emission Scanning Electron Microscope (FESEM) reveal surprisingly similar morphology and particle sizes for the zinc−copper matrix and the silica-supported zinc−copper matrix (Figure 4 top and bottom, respectively). The particle sizes lie between 50 and 500 nm, with most of the particles being oval or round and fewer being more plate-like and irregular.

EDS analyses of more than 20 individual regions of the silica-supported zinc−copper matrix identified two distinct compositions: those containing only zinc, oxygen, and silicon and those containing zinc, oxygen, copper, and silicon (in one individual analysis EDS was focused on the region within the box in Figure 5 on the left and right, respectively). The analysis is consistent with $Zn(OH)_2$ as the major phase in the matrix accompanied

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(44) Keen, D. A.; Hull, S. *J. Phys.: Condens. Matter* **1995**, *7*, 5793.

(45) Reference patterns were obtained from the powder diffraction file (PDF): $Zn(OH)_2$ reference code 01-089-0138; zinc metal reference code 01-087-0713, CuI reference code 01-083-1107.

(46) The Cu(K) peak appears because the sample is adhered to a double-sided conductive carbon tape.

(47) Reference patterns were obtained from the powder diffraction file (PDF): ZnO reference code 00-005-0664, CuO reference code 01-089-5899, Cu_3Zn reference code 03-065-6567.

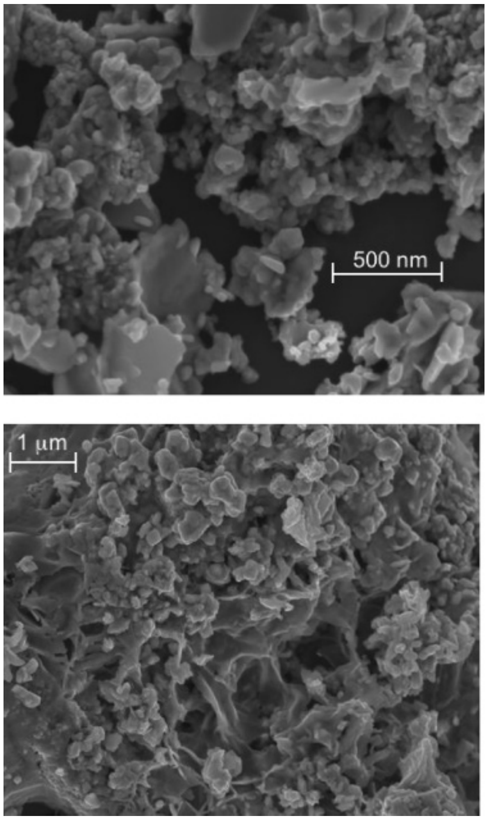


FIGURE 4. SEM Images of the zinc−copper matrix (top) and the silica-supported zinc−copper matrix (bottom).

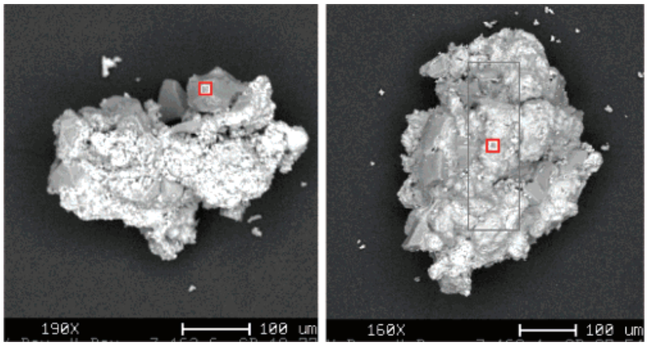


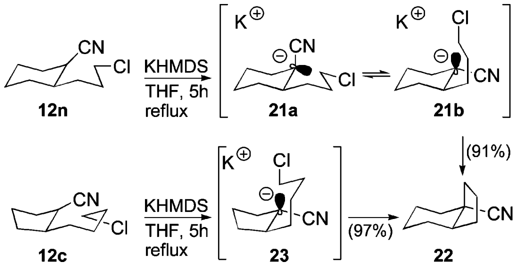
FIGURE 5. Electron microscope images of regions containing Zn−O−Si (left) and Zn−O−Cu−Si (right).

by a less abundant copper-containing phase comprised of zerovalent copper. Unfortunately no particles were identified[48] with copper alone, which is consistent with very small copper particles intimately mixed with $Zn(OH)_2$.

The material analyses consistently indicate that the reagent derived from elemental zinc and copper(I) iodide is comprised mainly of zinc hydroxide and a copper species that is most likely finely dispersed zerovalent copper, possibly in the form of nanoparticles. Powder diffraction and EDS data identify $Zn(OH)_2$ as the main zinc component with only a trace of elemental zinc. Stoichiometrically only half an equivalent of zinc is required for the reduction of copper(I) iodide to copper zero leaving the identity of the species undergoing oxidation by the remaining zinc somewhat obscure. Experimentally the reaction exhibits a precise requirement for zinc and copper in a 6:1 ratio, which possibly controls the particle size of the copper. Deviations from the 6:1 ratio afford a gray matrix tinged with a red hue suggesting formation of a different particle size with plasmon resonance different from that of the usual finely dispersed copper. Fortunately, adsorbing the copper species derived from a 6:1 ratio of elemental zinc and copper(I) iodide onto silica gel reproducibly provides an excellent reagent for the conjugate addition of alkyl iodides to alkenenitriles.

Metalated Nitrile Cyclizations. Conjugate additions of chloroalkyliodides with the silica-supported zinc−copper matrix affords chloroalkyl-substituted nitriles ideally poised for cyclization.[49] An extensive series of metalated nitrile S_Ni cyclizations demonstrates a profound sensitivity on solvent and metal cation, which suggests that deprotonating alkylnitriles with KHMDS in refluxing THF generate pyramidal, solvent-separated ion pairs.[50] In the case of nitrile **12n** deprotonation with KHMDS in refluxing THF affords the *cis*-hydrindane **22** exclusively (Scheme 5).[51] The stereoselectivity is consistent with cyclization of a pyramidal potassiated nitrile via conformation **21b**, which avoids the torsional strain incurred in the tether for cyclization through conformer **21a** to the corresponding *trans*-hydrindane. Similarly, cyclizing the analogous cyclohexanecarbonitrile **12c** under identical conditions affords the hydrindane **22**, presumably via the pyramidal potassiated nitrile **23**.

SCHEME 5. Metalated Nitrile Cyclizations to *cis*-Hydrindanes



In contrast to generating nitrile carbanions with KHMDS in refluxing THF, organocopper-substituted nitriles exhibit alkylation selectivities consistent with forming *C*-metalated nitriles.[52] The metal-dependent structural differences suggested an intriguing strategy for controlling the ring junction stereoselectivity simply by changing the metal cation. Attempts to redirect the cyclization stereoselectivity by generating the cuprated nitrile by sequential LDA deprotonation and transmetallation with MeCu revealed a surprisingly low reactivity of the putative *C*-cuprated nitrile **24** (Scheme 6). Refluxing **24** in THF fails to generate any of the hydrindane **22**! Cyclizing **24** requires the addition of silver tetrafluoroborate to coax displacement of the pendant electrophile, leading to the *cis*-hydrindane **22**. Despite the steric preference for orienting the small nitrile in the axial orientation,[53] no cyclization from conformer **24a** is observed.

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(48) Transmission electron miscroscopy coupled with EDS failed to locate individual copper particles.

(49) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.

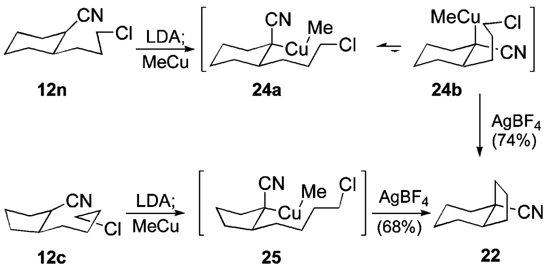
(50) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.

(51) For a related cyclization to an angular nitrile-containing *cis*-hydrindane see: Sato, M.; Suzuki, T.; Morisawa, H.; Fujita, S.; Inukai, N.; Kaneko, C. *Chem. Pharm. Bull.* **1987**, *35*, 3647. The *cis*-hydrindane stereochemistry was secured by hydrolysis to the corresponding amide and spectral correlation with a previously characterized sample: Molander, G. A.; Dowdy, E. D.; Schumann, H. *J. Org. Chem.* **1998**, *63*, 3386.

(52) Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200.

(53) The *A*-value of a nitrile is only 0.2 kcal mol^{-1}: Eliel, E. L.; Wilen, S. H.; Mander, L. N. in *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−7.

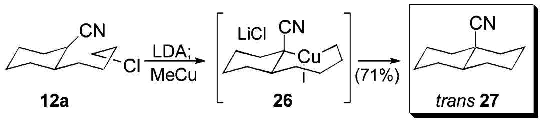
SCHEME 6. Cuprated Nitrile Cyclizations to *cis*-Hydrindanes



The *cis*-hydrindane **22** is the sole diastereomer detectable in the crude reaction mixture, which implies preferential cyclization through the more flexible conformation **24b** with the axial methyl copper. Relaxing the steric constraints by incorporating an additional carbon in the tether is insufficient to redirect the cyclization stereoselectivity since **12c** cyclizes exclusively to the *cis*-hydrindane **22** under identical conditions.

Employing a *C*-cuprated nitrile in the corresponding decalin cyclization with **12a** successfully redirects the cyclization to the *trans*-fused diastereomer **27** (Scheme 7). Sequential addition of LDA and MeCu to **12a** triggers cyclization to the *trans*-decalin **27** as the exclusive diastereomer.[54] For comparison, cyclizing **12a** with KHMDS in refluxing THF affords the *trans*-decalin **27** and the corresponding *cis*-decalin in a 6.3:1 ratio.[50] Exclusive formation of the *trans*-decalin **26** implies a distinctly different mechanism from the analogous cyclization with KHMDS and strongly suggests an equatorially oriented Cu(III) intermediate **26** as the reactive species.[55]

SCHEME 7. Cuprated Nitrile Cyclizations to *trans*-Decalin



Conclusion

The silica-supported zinc–copper matrix dramatically promotes conjugate additions of alkylhalides to acyclic and cyclic 5–7-membered alkenenitriles. Detailed mechanistic probes performed with primary alkyliodides are consistent with conversion to a radicaloid species by the zinc–copper matrix derived from elemental zinc and copper(I) iodide. Material characterization strongly implies that the reagent loosely referred to as a zinc–copper couple is actually finely dispersed, zerovalent copper.

Detailed material analyses provide insight into the nature of the zinc–copper matrix generated in the presence and absence of silica gel. Powder X-ray diffraction does not support the presence of coupled zinc and copper, but is silent on the exact identity of the copper species. The absence of a diffracting copper phase suggests either a noncrystalline form and/or small particles of copper, possibly nanocrystals, although the exact identity remains elusive. Powder X-ray diffraction, SEM, EDS, TGA, and ICP MS are consistent with the formation of an active copper species that is likely a zerovalent copper, but in the absence of definitive identification is best referred to as a zinc–copper matrix.

Depositing the active copper species onto silica gel dramatically facilitates the conjugate addition. Mechanistic probes are consistent with reduction of the alkyliodide to a radicaloid or a surface adsorbed radical that triggers conjugate addition to a proximal alkenenitrile. The silica gel is proposed to anchor the alkenenitrile in close proximity to the surface-adsorbed radicaloid through hydrogen bonding. Collectively, this methodology addresses the long-standing difficulty of conjugate additions to disubstituted alkenenitriles, demonstrates the dramatic influence of performing the reaction in the presence of silica gel, and provides insight into the nature of the reagent generated from elemental zinc and copper(I) iodide.

Experimental Section

General Conjugate Addition Procedure. Water (192 equiv) was added to a stirred mixture of Zn dust (3 equiv, 100 mesh) and powdered CuI (0.5 equiv). After 10 min, silica gel (27 equiv, 230–400 mesh) and additional water (192 equiv) were added in the optimized procedure, followed by the alkenenitrile (1 equiv). (The alkenenitrile was added directly in those reactions performed without silica gel.) After 15 min, the alkyliodide (1 equiv) was added, followed by seven sequential additions of the iodide (1 equiv) at 1 h intervals. Two additional infusions of Zn (3 equiv) and CuI (0.5 equiv) were added after 3 and 6 h with additional water (192 equiv) added during the last addition. The resulting mixture was stirred overnight and was then vacuum filtered through a glass fritted funnel. The crude product was then extracted with EtOAc, and the combined extracts were dried (Na_2SO_4), concentrated, and purified by radial chromatography (1:20 EtOAc/hexanes) to afford analytically pure material.

Octahydro-1*H*-indene-3a-carbonitrile (22). (a) Cyclization of 12n: A THF solution (1 M, 0.40 mmol) of KHMDS was added to a THF solution (10 mL) of **12n** (55 mg, 0.30 mmol) and the mixture was then heated to reflux. After 5 h the solution was cooled to rt, saturated aqueous NH_4Cl was added, and the organic phase was separated, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1:20 EtOAc/hexanes) to afford 40 mg (91%) of **22** as an oil: IR (film) 2231 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40–1.98 (m, 13H), 2.03–2.13 (m, 1H), 2.27–2.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.4, 22.7, 25.2, 27.4, 30.6, 36.6, 41.1, 44.0, 125.8; *m*/*e* 150 ($M + H^+$); HRMS (EI) calcd for $C_{10}H_{15}N^+$ 149.1199, found 149.1189. **(b) Cyclization of 12n via an organocopper:** A THF solution (1 M, 0.26 mmol) of LDA was added to a −78 °C, THF solution (10 mL) of **12n** (50 mg, 0.27 mmol). After 1 h, a THF solution (5 mL) of BuCu, made from a hexanes solution (2.7M, 0.32 mmol) of BuLi and anhydrous CuI (62 mg, 0.32 mmol), was added followed by solid $AgBF_4$ (50 mg, 0.26 mmol). The reaction mixture was allowed to warm to rt and after 16 h, saturated aqueous NH_4Cl was added. The aqueous phase was then separated and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:20 EtOAc/hexanes) to afford 30 mg (74%) of **22** as an oil. **(c) Cyclization of 12c:** A THF solution (1 M, 0.43 mmol) of KHMDS was added to a THF solution (10 mL) of **12c** (66 mg, 0.36 mmol) and the mixture was then heated to reflux. After 5 h the solution was cooled to rt, saturated aqueous NH_4Cl was added, and the aqueous phase was then separated and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:20 EtOAc/hexanes) to afford 51.4 mg (97%) of **22**. **(d) Cyclization of 12c via an organocopper:** A THF solution (1 M,

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(54) ^{1}H NMR analysis of the crude reaction mixture failed to identify any of the diastereomeric *cis*-decalin.

(55) Analogous Cu(III) species were verified as key intermediates during coupling of lithium dimethyl cuprate with halobenzenes,[a] although the lifetime of this intermediate may be short since a Cu(III) intermediate was not detected by ^{13}C NMR during the reaction of Me_2CuLi with 1-bromocyclooctene.[b] (a) Spanenburg, W. J.; Snell, B. E.; Su, M.-C. *Microchem. J.* **1993**, *47*, 79. (b) Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 12264.

0.26 mmol) of LDA was added to a −78 °C, THF solution (10 mL) of **22** (48 mg, 0.26 mmol). After 1 h, a THF solution (5 mL) of MeCu, made from a hexanes solution (1.6 M, 0.31 mmol) of MeLi and anhydrous CuI (59 mg, 0.31 mmol), was added, followed by solid $AgBF_4$ (60 mg, 0.31 mmol). The reaction mixture was allowed to warm to rt and after 16 h, saturated aqueous NH_4Cl was added. The aqueous phase was then separated and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:20 EtOAc/hexanes) to afford 26 mg (68%) of octahydro-1*H*-indene-3a-carbonitrile as an oil. Basic hydrolysis of **22** (34.0 mg, 0.23 mmol) with excess NaOH in ethylene glycol at ∼240 °C for 6 h afforded 7 mg (20%) of octahydro-1*H*-indene-3a-carboxamide (**i**) as a white solid spectrally identical with previously characterized material.[51]

Decahydronaphthalene-4a-carbonitrile (27). A THF solution (1 M, 0.26 mmol) of LDA was added to a −78 °C, THF solution (15 mL) of 2-(4-chlorobutyl)cyclopentanecarbonitrile (125 mg, 0.62 mmol). After 1 h, a THF solution (5 mL) of MeCu, made from a hexanes solution (1.6 M, 0.75 mmol) of MeLi and anhydrous CuI (143 mg, 0.75 mmol), was added. The reaction mixture was allowed to warm to rt and after 16 h, saturated aqueous NH_4Cl was added. The aqueous phase was then separated and extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1:20 EtOAc/hexanes) to afford 73 mg (71%) of *trans*-decahydronaphthalene-4a-carbonitrile spectroscopically identical with material previously isolated.[50]

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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