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Forming Tertiary Organolithiums and Organocuprates from Nitrile Precursors and their Bimolecular Reactions with Carbon Electrophiles to Form Quaternary Carbon Stereocenters**

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The stereoselective formation of quaternary carbons is one of the most demanding challenges in organic synthesis.[1] An especially direct way to construct such stereocenters would be to combine a prochiral tertiary organometallic and a carbon-centered electrophile (Figure 1A). However, this strategy is not mentioned in the numerous reviews of stereoselective synthesis of chiral quaternary carbons,[1] and to our knowledge has never been employed in target-directed organic synthesis. This omission undoubtedly derives from the

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challenge in generating tertiary organometallic intermediates, particularly those containing three alkyl substituents.[2–4] We were recently drawn to explore this undeveloped approach for forming quaternary carbon stereocenters in the context of fashioning the demanding C8–C14 bond and the C8 quaternary stereocenter of rearranged spongian diterpenes such as aplyviolene (**4**) and dendrillolide A (**5**) by the reaction of tertiary organocuprate **1** and cyclopentenone **2**. This coupling was anticipated to take place from the convex face of nucleophile **1** and from the face of **2** opposite the branched side chain (Figure 1B).[5]

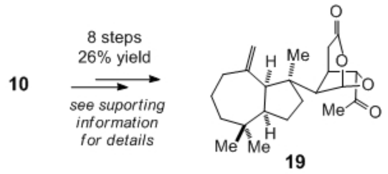
We report herein that a) unstabilized tertiary organolithium intermediates can be conveniently generated by reductive decyanation of nitrile precursors and that these reagents and their derived cuprates couple in useful yields with carbon-centered electrophiles, b) chiral tertiary organolithium and organocuprate intermediates in the *cis*-perhydroazulene and *cis*-perhydropentalene series react with electrophiles with high diastereoselectivity from the ostensibly more-hindered concave face, and c) computational studies that suggest the origin of this unexpected diasteroselectivity.

Reductive lithiation of C–X bonds is widely practiced to generate organolithium intermediates,[6] with reductive lithiation using lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB) having been employed to produce achiral tertiary organolithium intermediates from chloride, bromide and sulfide precursors.[7–9] We conjectured that chiral tertiary nitriles, which are more readily synthesized than tertiary halides or sulfides, might constitute useful progenitors of chiral tertiary organolithium reagents. Many α-heterosubstituted lithium reagents—including fully substituted ones—have been formed from nitrile precursors and trapped with carbon-centered electrophiles to yield valuable products;[10] moreover, the generation of an assortment of tertiary-benzylic lithium intermediates from benzylic nitrile precursors and their bimolecular trapping has also been reported.[11] Nonetheless, whether less-stable trialkyl tertiary organolithium intermediates could be generated from nitrile precursors and subsequently trapped was unknown, and had been suggested might not be feasible.[11] Encouraged by Rychnovsky's reductive formation of one such intermediate and its intramolecular trapping,[12] we chose to examine whether unstabilized tertiary lithium reagents and their derived cuprates[13] could be generated from nitrile precursors and trapped in bimolecular reactions with carbon-centered electrophiles.

Initially we investigated the formation of simple tertiary organolithium intermediates from six tertiary nitrile precursors. After considerable optimization, the following procedure was found to be effective: the tertiary nitrile (1.5 equiv) was added rapidly to 3 equiv of freshly prepared LiDBB[14] in THF at −78 °C, followed 1 min later by the addition of 1.0 equiv of an aldehyde. A variety of neopentylic alcohols could be prepared in this way in useful yields, with the presence of alkene, alkyl ether, triisopropylsilyl ether (but not *tert*-butyldimethylsilyl ether), and electron-rich aromatic rings being tolerated (Table 1).

The conversion of reductively generated tertiary organolithium intermediates to tertiary organocuprates, and the use of the latter in conjugate reactions, was investigated next. After exploring the formation and reactivity of various lithium and dilithium organocuprates, we settled on dilithium cyanocuprates containing a "non-transferable" trimethylsilylmethyl substituent.[15] In the optimized procedure, a THF solution of $Me_3SiCH_2CuCNLi$ (generated from trimethylsilylmethyllithium and copper cyanide) was added rapidly to the freshly prepared tertiary organolithium intermediate at −78 °C, and, after 5 min, a THF solution of an enone and a trialkylsilyl chloride was added.[16] In this way, eight diverse 3-substituted cyclohexanones **6** were formed in yields of 56–75% (Table 2). In addition, three *trans*-cyclopentenoxysilane adducts **7** were prepared in good yields (51–81%) and >20:1 diastereoselectivities by the reaction of tertiary organocuprate intermediates with cyclopentenone **2**.

To explore whether this chemistry could be used to form quaternary stereocenters, we examined its utility in the pivotal fragment coupling step of the projected total syntheses of aplyviolene (**4**) and dendrillolide A (**5**) depicted in Figure 1B. Salient results of our investigation of the reactivity of tertiary organolithium and organocuprate reagents generated from *cis*-perhydroazulene nitriles **8** and **9** are summarized in Scheme 1.[17] We were delighted to find that the organocuprate intermediate derived from nitrile **8** reacted with cyclopentenone **2** to give a single coupled product **10** in 70% yield. To our surprise, the relative configuration of this product showed that electrophilic addition had taken place with high stereoselectivity from the concave face of the *cis*-perhydroazulene nucleophile.[18] To gain insight into the possible origin of this unexpected diastereoselection, the lithium reagent generated from nitrile **8** was quenched with methanol to give largely one hydrocarbon product; ^{1}H NMR nOe analysis of the derived ketone **11** established that protonation of the tertiary organolithium intermediate also took place with high stereoselectivity from the concave face.[19] In a similar fashion, carboxylation of the lithium reagent generated from nitrile **8**, or from epimeric nitrile **9**, took place from the concave face to give carboxylic acid **12** in >20:1 diastereoselectivity. The selective formation of carboxylic acid **14** from saturated nitrile precursor **13** shows that the exomethylene group plays at most a minor role in the facial selectivity of the reaction of chiral tertiary lithium reagents in this series.[20]



Reductive decyanation was also used to generate analogous unstabilized tertiary organolithium and organocuprate intermediates in the *cis*-perhydropentalene series (Scheme 2). Reductive lithiation of *cis*-perhydropentalene nitrile **15** and quenching with methanol or carbon dioxide gave hydrocarbon **16** (dr = 2.6:1) or carboxylic acid **17** (dr = 4.1:1), with the major isomer in each case arising from preferential reaction from the concave face of the *cis*-perhydropentalene nucleophile.[21 , 22] In addition, nitrile **15** was converted to an organocuprate and coupled with methyl vinyl ketone to give **18**, again with reaction occurring preferentially from the concave face.[23,24]

The results summarized in Schemes 1 and 2 show that the tertiary lithium and cuprate reagents in these *cis*-bicyclic ring systems react with electrophiles preferentially from the concave face in an apparently electrophile-independent fashion. As organolithium intermediates typically undergo protonation by $S_E2$ret pathways,[3,25] the observation that the lithium reagents formed from nitriles **8**, **9**, and **15** protonate from the concave face indicates that lithium preferentially resides on the concave face of these *cis*-bicyclic ring systems. Computational studies were undertaken to gain further insight into the origin of this preference.

To this aim, the thermodynamic stability of different intermediates occurring after the proposed decyanation and reduction of the radical species with LiDBB, were evaluated at the B3LYP/6-31+G(d,p) level.[26] Both naked carbanionic (**8**-an, **15**-an) and organolithium (**8**-Li, **15**-Li) species derived from *cis*-perhydroazulene and *cis*-perhydropentalene precursors **8** and **15**, respectively, were considered. In accordance with the experimental conditions and related computational[27] and X-ray[28] data, only monomeric species were considered and lithium was solvated with three discrete dimethyl ether molecules. Both epimers at the reacting center (labelled as α,β) and all possible ring conformations were considered, in order to obtain theoretical diastereomeric ratios based on Boltzmann distributions at 298 K estimated from relative enthalpies (ΔH) of these intermediates.[29] Activation enthalpies ($\Delta H^{\ddagger}$) for the pyramidal inversion of naked carbanions (**8**-inv, **15**-inv), were also calculated. For comparison, the relative enthalpies of epimeric carboxylated (**12**-CO_2^-, **17**-CO_2^-) and protonated products, expressed as diastereomeric ratios, were also calculated.[30]

In good agreement with experimental observations, these calculations revealed a greater stability of those species bearing either the lone-electron pair or the lithium atom on the concave faces (>1.7 and >0.5 kcal mol^{-1} for perhydroazulene and perhydropentalene derivatives, respectively, Table S1, supporting information). The neutralization of the negative charge with bulky solvated Li cations provides diastereomeric ratios closer to the experimental data, proving to be a more realistic model. Conversely, values derived from naked anions look slightly overestimated, in particular for perhydropentalene **15**-an. In addition, the calculated lowest barriers for the epimerization of the carbanionic species were perfectly feasible under the reaction conditions (4.0 and 9.1 kcal mol^{-1} for **8**-inv, **15**-inv, respectively). As the formation of contact ion pairs (*i.e.* organolithium) are likely nearly barrierless processes, it is conceivable that the rapid equilibration of such metalated species can also occur through the aforementioned inversion transition structures.

These studies support the notion that observed selectivity is independent of the ground state energy of the diastereomeric products. Whereas the epimeric protonated products showed similar calculated energies, the, bulkier CO_2^- moieties are preferentially positioned on the less-hindered convex face by 2.3 and 0.7 kcal mol^{-1} for the *cis*-perhydroazulene and *cis*-perhydropentalene carboxylate products, respectively (Table S1). Although the $[Li(OMe_2)_3]^+$ units are indeed bulkier than CO_2^-, they are placed at a much larger distance (~2.1 Å) than the covalent C–C bond formed in the product (~1.6 Å), minimizing steric interactions.

The observed stereoselectivities can be easily rationalized by torsional strain considerations (Figure 2). As seen in the minimum energy structures of *cis*-perhydroazulene organolithium epimers **8**-Li-**α** and **8**-Li-**β** depicted in Figure 2, in each epimer the methyl substituent at the reacting center resides in an equatorial position in order to avoid s*yn*-pentane repulsions with the fused ring. In addition, the seven-membered and five-membered rings adopt nearly optimal conformations in both epimeric intermediates. However, there are significant differences in the dihedral angles around the bridgehead carbons in the two epimers. Inspection of Newman projections along the C1–C2 and C3–C4 bonds of the lithiated five-membered ring (labelled with blue and red dots in Figure 2 insets, respectively) indicates that **β** epimers are more eclipsed then the **α** ones, reflected by smaller dihedral angles.[31] Such effects have been reported previously to govern the stereoselectivities in a wide variety of situations.[32] Eclipsing and staggering around the bonds attached to the two bridgehead carbons of **8**-Li are correlated. Thus, C3–C4 is eclipsed and C1–C2 is staggered in less stable 8-Li-**β**, while C3–C4 is staggered and C1–C2 is eclipsed in more stable **8**-Li-**α**. As the C2–Li bond is quite long in these intermediates, it is unlikely that the eclipsing involving these atoms contributes significantly to instability. Instead, the conformation around the C3–C4 bond appears to be more important.

In summary, we have developed a general procedure for the synthesis of tertiary trialkyl-substituted organolithiums and organocuprates and employed these intermediates in the stereocontrolled construction of quaternary carbon stereocenters. Tertiary *cis*-perhydroazulene and *cis*-perhydropentalene lithium and cuprate intermediates react with carbon electrophiles with high diastereoselectivity from the sterically more-hindered concave face. Theoretical studies suggest that the thermodynamic preference for the residence of both a naked carbanion or lithium species on the concave faces of such systems dictate the observed stereoselectivity. Differential torsional strain occurring at the bridgehead atoms towards the five-membered ring is at the origin of this stability pattern. The application of prochiral tertiary organometallic and related radical intermediates[22] for fragment coupling in the stereocontrolled synthesis of natural products containing quaternary carbon stereocenters is under current investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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17. For details of the synthesis of these nitriles, see the supporting information.
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19. Identical results were realized with epimeric nitrile **9**; see supporting information for details.
20. See supporting information for the preparation of nitrile **13**.
21. The synthesis of nitrile **15** and the methyl epimer of product **18** is reported in the accompanying paper.[22]
22. Schnermann, MJ.; Overman, LE. following communication in this issue.
23. In this instance, the trimethylsilylmethyl ligand underwent competitive addition to methyl vinyl ketone and a homocuprate was employed.
24. The impact of additives (TMEDA, HMPA, $MgBr_2$, $ZnCl_2$) and reaction temperature was examined in the protonation of the organolithium intermediates derived from nitriles **9** and **15**. Diastereoselection was not significantly modified in any of these efforts, although the scope of these studies was limited by the highly reactive nature of the tertiary organolithium intermediates and the requirement that THF be used as the solvent for the arene-radical anion-mediated lithiation.[14]
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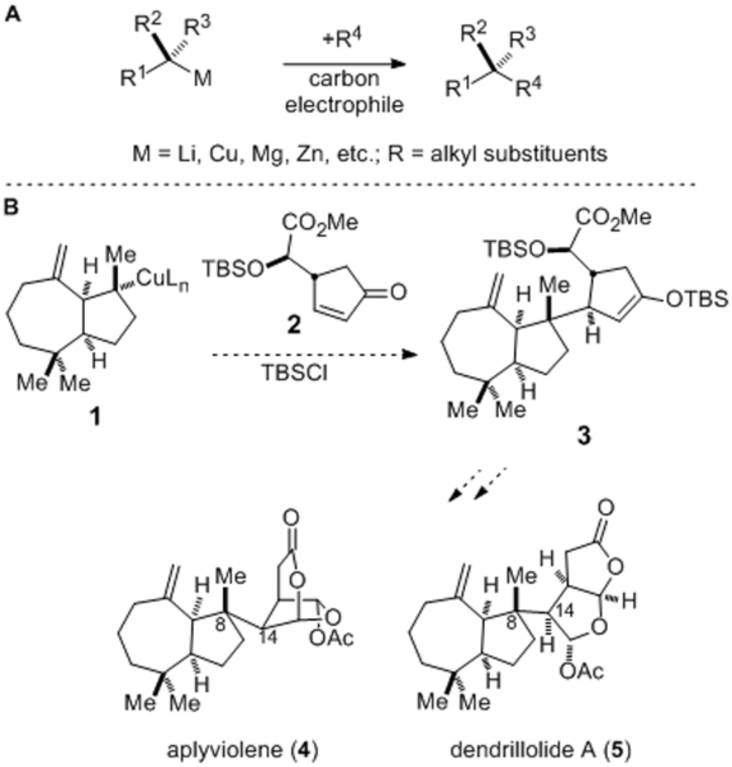
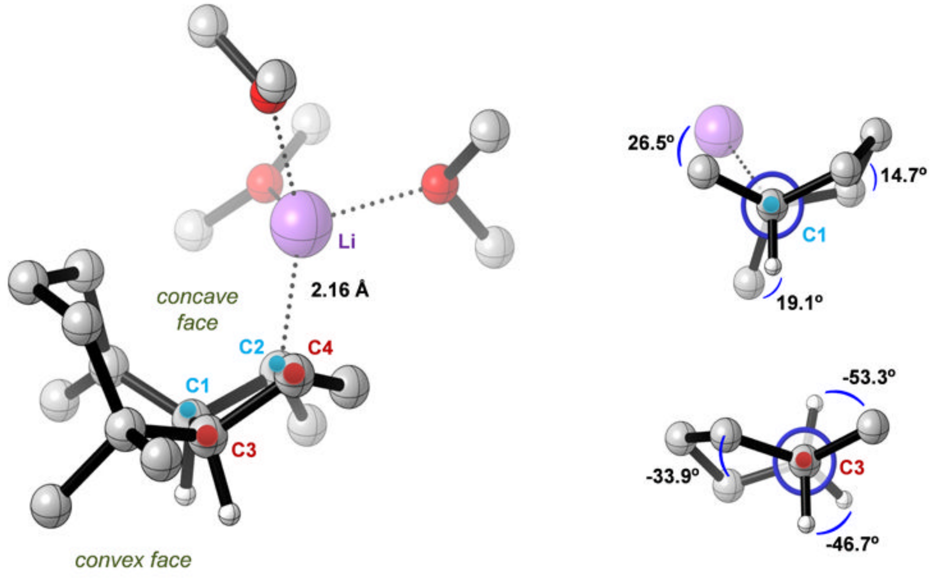
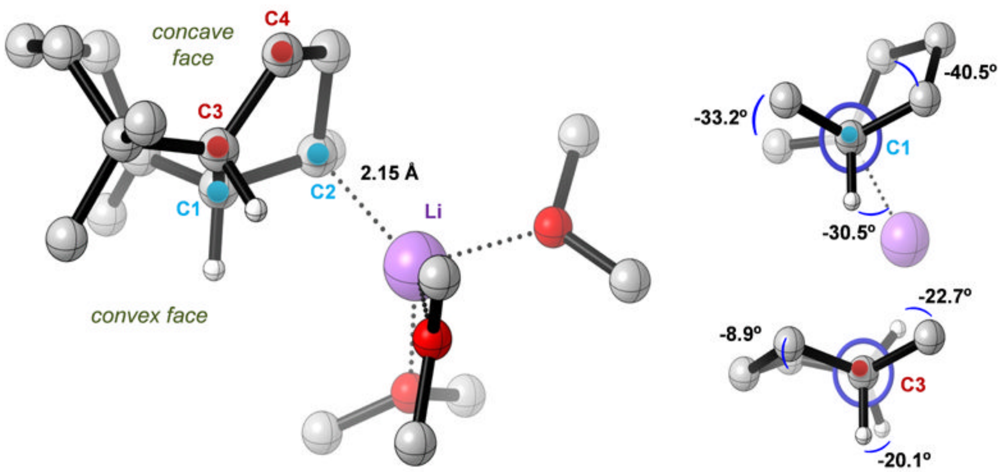


Figure 1.

Forming quaternary carbon stereocenters by the reaction of prochiral tertiary organometallics and a carbon-centered electrophile (A) and the potential use this strategy to synthesize rearranged spongian diterpenes such as aplyviolene and dendrillolide A (B).



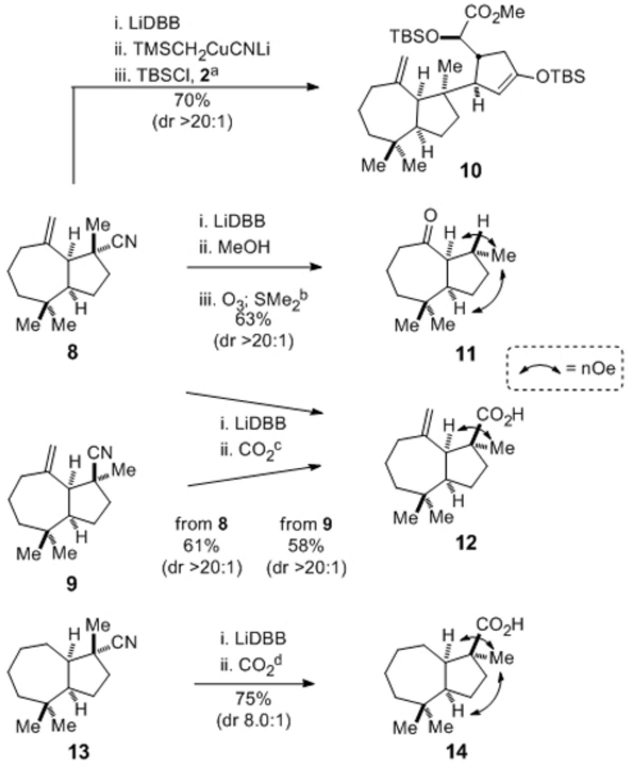
5-Li-**α** (ΔΔH = 0.0 kcal mol^{-1})



5-Li-**β** (ΔΔH = 1.7 kcal mol^{-1})

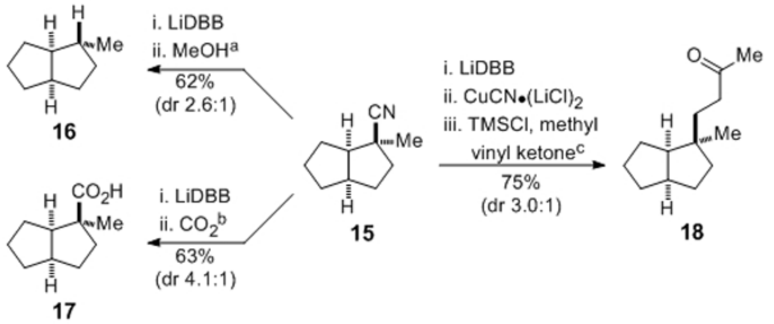
Figure 2.

Optimized structures of solvated organolithium intermediates derived from perhydroazulene nitrile **8** after reductive lithiation. The Newman projections of interest (shown as insets) are viewed from the C1→C2 and C3→C4 directions. Relative enthalpies calculated at the B3LYP/6-31+G(d,p) level are displayed.



Scheme 1.

Reductive lithiation/electrophilic trapping of chiral *cis*-perhydroazulene nitriles **8**, **9**, and **13**: [a] **8** (2.0 equiv), THF, −78 °C; LiDBB (4.0 equiv), 30 sec; TMSCH$_2$CuCNLi (2.0 equiv), 5 min; 1.0 equiv **2**, TBSCl (5.0 equiv), in THF, 1 h. [b] **8**, THF, −78 °C; LiDBB (2.2 equiv), 30 sec; MeOH; O$_3$, CH$_2$Cl$_2$: MeOH, 78 °C; dimethyl sulfide. [c] **8** or **9**, THF, −78 °C; LiDBB (2.2 equiv), 30 sec; CO$_2$; 1 N HCl. [d] as c but with **13**.

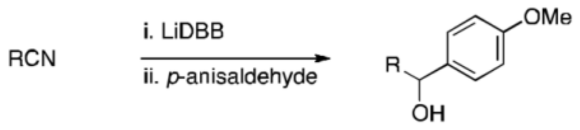


Scheme 2.

Reductive lithiation and reactivity of *cis*-perhydropentalene nitrile **15**: [a] **15**, THF, −78 °C; LiDBB (2.2 equiv), 30 sec; MeOH. [b] **15**, THF, −78 °C; LiDBB (2.2 equiv), 30 sec; CO_2; 1 N HCl. [c] **15 (**4.0 equiv), THF, −78°C; LiDBB (8.0 equiv), 30 sec; $CuCN\text{-}(LiCl)_2$ (2.0 equiv), 5 min; TMSCl (5.0 equiv); methyl vinyl ketone in THF, 1 h; 1 N HCl.

Table 1

Trapping of tertiary organolithium intermediates derived from nitriles with *p*-anisaldehyde.[a]



Entry	R	Yield [%]
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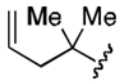
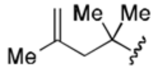
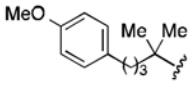
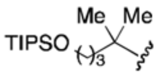
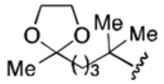
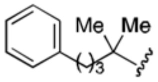
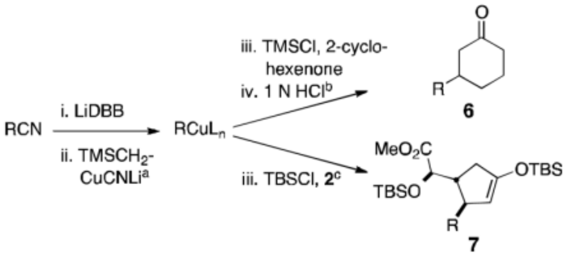
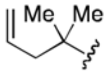
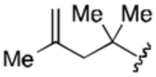
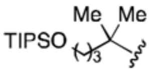
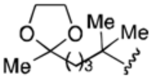
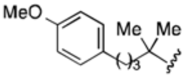
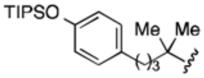
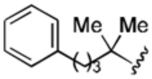
2		73
3		66
4		71
5		61
6		59
7		70

[a] Conditions: 1.5 equiv nitrile, 3.0 equiv LiDBB, −78 °C, 1 min; 1 equiv aldehyde. LiDBB = lithium di-*tert*-butylbiphenylide. TIPS = triisopropylsilyl.

Table 2

1,4-Addition of tertiary organocuprates derived from tertiary nitriles to cyclohex-2-en-1-one or enone **2**.



Entry	R	Yield 6 [%]	Yield 7 [%]
1	*t*Bu	71	78[e]
2		63	
3		56	51[e]
4		75	
5		70[d]	
6		72	
7		60	81[f]
8		67	

[a] Conditions: 2.0 equiv nitrile, 4.0 equiv LiDBB, −78 °C, 30 sec; 3.1 equiv $TMSCH_2CuCNLi$, 5 min.

[b] Conditions: 1.0 equiv 2-cyclohexenone, 5.0 equiv TMSCl, −78 °C, 1 h; 1 N HCl, RT.

[c] Conditions: 1.0 equiv **2**, 2.0 equiv TBSCl, −78 °C, 1 h.

[d] Isolated as the silyl enol ether.

[e] 2.5 equiv of $TMSCH_2CuCNLi$ used in a.

[f] 2.0 equiv of $TMSCH_2CuCNLi$ used in a and 5.0 equiv of TBSCl in c. TMS = Trimethylsilyl. TBS = *tert*-butyldimethylsilyl.