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Conjugate addition reactions of α-azoalkylcuprate reagents

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Abstract

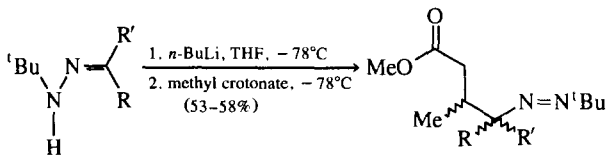
A new class of α-heteroatomalkyl organocuprate/organocopper reagents has been prepared. These α-azoalkyl cuprate reagents were derived from α-azoalkyl anions and were treated with enones and enoates affording γ-azoalkyl carbonyl compounds in modest yields.

Keywords: Organocuprate; Organocopper; α-Azoalkyl cuprate; α-Aminoalkyl cuprate conjugate addition; α-Azoalkyl anion; Enone

1. Introduction

Organocopper reagents are one of the most synthetically powerful and widely used reagents for the construction of carbon–carbon bonds beta to a carbonyl functionality. In recent years there has been an increased effort to transfer highly functionalized ligands in conjugate addition reactions to α,β-alkenyl carbonyl compounds [1]. The ability of organocopper reagents to transfer α-heteroatom alkyl ligands such as α-alkoxy [2] and α-thioalkoxy [3] has received varied attention. Recently, we have demonstrated that α-aminoalkylcuprates participate in 1,4-addition reactions in good to excellent yields [4].

Lithiated α-azoalkyl carbanions [5,6] derived from *tert*-butylhydrazones, in turn prepared from ketones and aldehydes, have been examined as nucleophiles in a 1,4-addition reaction (Eq. 1) to methyl crotonate [5]. However, the reaction gave only good to modest yields of conjugate addition adducts and was limited to methyl crotonate. We anticipated that reaction of the α-azo carbanion with a copper (I) salt would produce a copper reagent which might enhance the ability of the α-azoalkyl carbanion synthon to participate in conjugate addition reactions. However, it was unknown whether the cuprate reagents would effectively work because the ambident nature of the allylic anion (carbanion vs. amide anion). If the regioselectivity of the ambident anion could be controlled during cuprate formation, then this procedure would provide a direct entry to α-azoalkyl cuprates, a potentially useful subset of nitrogen based α-heteroatomalkyl cuprates.



(1)

2. Results

The study was initiated by examining the *tert*-butyl hydrazone of acetaldehyde **1** (Eq. 2). Lithiation of **1** (^{n}BuLi, THF) [5,6] afforded the corresponding α-azoalkyl carbanion which was allowed to react with CuSPh [7] (THF at −25– − 30 °C) to afford a homogenous brown-yellow solution. Treatment of the resultant cuprate with 2-cyclohexen-1-one resulted in 1,4-addition (Table 1, entry 1) giving largely one product (61% yield). Purification by radial chromatography afforded a 23–33% yield of adduct **2**. Using diethyl ether as the solvent, a 71% crude recovery of the conjugate addition adduct was obtained and purification yielded 20% (Table 1, entry 2). Treatment of RCuSPhLi (from lithio-**1**) with methyl vinyl ketone gave a complex mixture of products. Reaction of RCuSPhLi derived from lithio-**1** with sterically hindered α,β-enones (e.g., isophorone, 3-methyl-2-cyclopenten-1-one and mesityl oxide) in THF gave either unreacted enone or a com-

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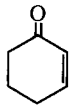
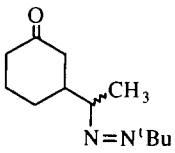
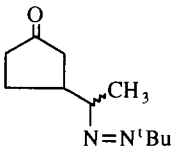
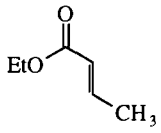
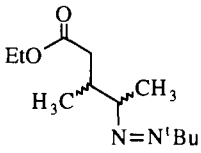
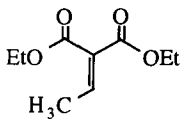
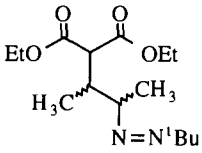
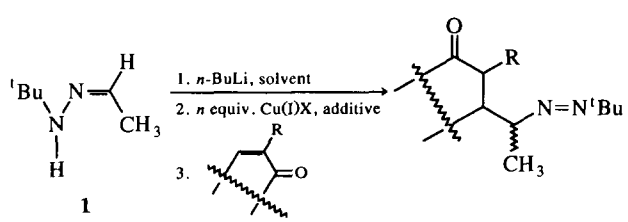
Table 1
Conjugate addition of α-azoalkyl organocopper reagents derived from *tert*-butyl hydrazone **1** to α,β-enones and enoates depicted in Eq. 2

Entry	Substrate	Copper reagents	Solvent	% Yield (crude) [a]	% Yield (pure) [b]	Product and diastereoselectivity
						 **2**
1		RCuSPhLi	THF	61	23–33	54:45 [c]
2			Et_2O	71	20	30:69 [c]
3		$RCuNEt_2Li$	THF	62	42	40:59 [c]
4		RCu · TMEDA	THF	83	– [d]	
5		$RCu \cdot P^nBu_3$	Et_2O	–	5 [e]	53:47 [c]
						 **3**
6		$RCuNEt_2Li$	THF	67	15 [e]	36:63 [c]
7		RCu · TMEDA	THF	85	61	64:35 [c]
						 **4**
8		RCuSPhLi	THF	69–88	37–46	35:64 [f]
						 **5**
9		RCuSPhLi	THF	84	31	40:59 [g]

[a] Represents weight percent of recovered crude reaction material which contained minor impurities (≥ 90% pure) by ^1H NMR analysis.
[b] Isolated yield. The azo products were unstable to chromatographic purification used to obtain analytically pure samples.
[c] Diastereoselectivity based on peak height of the γ-CH_3 absorption in the ^{13}C NMR spectrum.
[d] No purification attempted.
[e] Sample had begun to decompose upon storage.
[f] Diastereoselectivity based on peak height of the carbonyl resonance in the ^{13}C NMR spectrum.
[g] Diastereoselectivity based on the peak height of C-3 or C-4 in the ^{13}C NMR spectrum.

plex mixture of compounds. RCuSPhLi prepared in Et_2O from lithio-**1** failed to react with isophorone as the substrate and starting material were recovered.



1 (2)

The diethylamidocuprate reagent, $[RCuNEt_2Li]$, was examined as well. The amidocuprate derived from lithio-**1** ($^tBuN = NCHLiCH_3$) was prepared from ($CuNEt_2 \cdot LiI$) in THF. Upon treatment with 2-cyclohexen-1-one, an 83% crude recovery of a moderately clean reaction product was obtained (Table 1, entry 3). Purification by radial chromatography afforded a 42% yield of **2**. Additionally, 2-cyclopenten-1-one was reacted with the amidocuprate to afford a 67% crude recovery of **3** which was also moderately clean by spectroscopic analysis (Table 1, entry 6). A 15% yield of **3** was obtained after radial chromatography of a

sample that had partially decomposed. The diethyl amidocuprate prepared in THF or Et_2O and reacted with methyl vinyl ketone afforded a complex mixture of products.

Alkyl copper reagents were also examined. The alkyl copper reagent, $^nBu_3P \cdot CuR$ [8], [($^nBu_3P \cdot CuI$) + $^tBuN{=}NCHLiCH_3$ (lithio-**1**)] was prepared in diethyl ether and treated with 2-cyclohexen-1-one. Conjugate addition was indicated by analytical TLC and by IR analysis; however, a clean sample mixture could not be obtained owing to sample contamination by $^nBu_3P$. Attempted removal of the phosphine from the 2-cyclohexen-1-one adduct **2** was not successful even with filtration through a silica gel column. Radial chromatography of a sample that displayed decomposition afforded only a 5% yield of **2** (Table 1, entry 5).

Additionally, an alkyl copper reagent (RCu · TMEDA + TMSCl) [9] was prepared from lithio-**1** in THF. Treatment of this reagent with 2-cyclohexen-1-one gave a mixture of the trimethyl silyl enol ether 1,4-adduct and unreacted enone. Reaction of 2-cyclopenten-1-one with the Johnson type reagent similarly afforded a mixture of the trimethylsilyl enol ether and saturated ketone 1,4-adducts. Upon standing, the silyl enol ether product slowly hydrolyzed to the saturated ketone adduct **3** (approximate 85% crude recovery was achieved after filtration through a neutral alumina plug using ethyl acetate and petroleum ether). After purification, **3** was obtained in 61% yield (Table 1, entry 7). Additionally, reaction of 3-methyl-2-cylcopenten-1-one, a modestly sterically hindered enone, resulted in a complex reaction mixture void of any desired product.

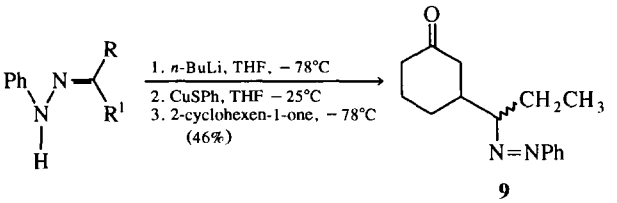
Reaction of ethyl crotonate with RCuSPhLi derived from hydrazone **1** gave a moderately clean conjugate addition product **4**. A 69–88% crude recovery of **4** was obtained and the adduct was isolated in 37–46% yield (Table 1, entry 8). Reaction of RCuSPhLi in THF with 2-ethylidene diethyl malonate (Table 1, entry 9) afforded a 84% crude recovery and purification of **5** gave a 31% yield. Treatment of the RCuSPhLi with other esters (e.g., ethyl methacrylate, methyl 1-cyclohexene-1-carboxylate and ethyl sorbate) did not give any desired conjugate addition products.

Overall, the isolated yields of the 1,4-adducts were modest (5–61%); however, the yields based on the crude 1,4-adducts were good (61–88%). The crude samples appeared clean by ^1H NMR and could be utilized for other potential syntheses without the need of further purification. The reduction in isolated yield compared to the crude yield is attributed to the instability of the azo products to chromatographic purification.

Conjugate addition of the α-azoalkyl group (derived from lithio-**1**) to β-substituted enones or enoates afforded mixtures of diastereomers (Table 1; vide supra), displaying poor to moderate diastereoselectivity. Although the ratio of diastereomers was affected by the nature of the reagents (Table 1, entries 1, 3–5, 6, and 7) and solvent (Table 1, entries 1 and 2), the small deviation from a 1 : 1 mixture was not synthetically useful.

Attempts to convert the resulting γ-azoketones to 1,4-diketones were problematic. Conditions set forth by Baldwin and coworkers (1. trifluoracetic acid, CH_2Cl_2, room temperature 2. aqueous oxalic acid) [5] afforded complex mixtures as determined by analytical TLC and ^1H NMR analysis when attempted with the 2-cyclohexen-1-one adduct. Additionally, hydrogenolysis of the γ-azoester functionality using H_2/Raney-nickel along with sonication [10] did not afford any of the desired γ-amino carbonyl adducts.

Phenyl hydrazones derived from aldehydes or ketones participate in ene reactions and the resulting phenyl azo adducts could be transformed into either ketones or amines [5]. In an effort to exploit this ability to transform the azo adduct into a free amine, and to circumvent the problematic transformation of the *tert*-butyl azo moiety to a synthetically useful functionality, the phenyl hydrazones **6**, **7**, and **8** were explored in conjugate addition reactions with 2-cyclohexen-1-one. Lithiation of the phenyl hydrazones in THF should give an ambident allyic anion which can potentially react with an electrophile at either carbon or nitrogen. Utilization of phenyl hydrazones affords allylic anions which undergo reaction on nitrogen rather than carbon [5a] which contrasts to the allylic anion prepared from the *tert*-butylhydrazones.



9

R = H, R¹ = Et **6**
R = H, R¹ = Ph **7**
R = R¹ = Me **8**

(3)

Preparation of the cuprate reagent from lithiated-**6** and CuSPh and subsequent treatment with 2-cyclohexen-1-one afforded conjugate addition adduct **9** in 46% yield (Eq. 3). The diastereoselectivity of this reaction could not be determined from the NMR spectra. Phenylthiocuprates were prepared from lithiated-**7** and **8** in THF and treated with 2-cyclohexen-1-one, but no reaction was observed. Additionally cyanocuprates (2RLi + CuCN) in THF were prepared from lithiated-**6** and **7** and treated with 2-cyclohexen-1-one and no reaction was observed. When the cyanocuprates were treated with 2-cyclohexen-1-one and five equivalents of chlorotrimethylsilane, complex reaction mixtures were obtained.

3. Discussion

The problems encountered by Baldwin [5] in the ability of lithio-α-azoalkyl carbanion derivatives to participate in 1,4-addition reactions with α,β-enones and α,β-enoates appears to be alleviated, in part, by utilization of α-azoalkylcopper or cuprate reagents (cf. Table 1). However, sterically hindered enones (e.g., mesityl oxide, 3-methyl-2-cyclohexen-1-one, and isophorone) failed to react with α-azoalkyl cuprate and copper reagents under a variety of conditions.

The phenylthiocuprate reagent and amidocuprate derived from **1** underwent conjugate transfer of an α-azoalkyl ligand to α,β-enones in modest yields (cf. Table 1). The data obtained from a limited number of experiments suggested that the $RCuNEt_2Li$ reagent was comparable in reactivity to the RCuSPhLi reagent. Additionally, these two copper reagents were attractive because they required only one equivalent of the α-azoalkyl ligand for cuprate preparation.

The Johnson type alkyl copper reagent (RCu · TMEDA + TMSCl) reacted with both 2-cyclohexen-1-one and 2-cyclopenten-1-one to give 1,4-addition reactions (cf. Table 1) in good yield. This reagent also allowed for conservation of the α-azoalkyl ligand. The use of a phosphine stabilized alkyl copper reagent ($RCu \cdot PBu_3$) appeared moderately effective. However, the drawback to this reagent was the removal of the phosphine from the 1,4-addition adducts which required tedious chromatographic separations.

The phenylthiocuprate reagent underwent 1,4-addition to α,β-enoates in modest yields (cf. Table 1). The reagent appears to be limited by substrate structure, but the use of this reagent does allow for the conservation of one equivalent of the α-azoalkyl ligand. By using activated enoates, e.g. alkylidene malonates, the problem of substrate reactivity may be alleviated, as shown by entry 9, allowing for generalization of the conjugate addition to enoates.

The generally positive reactivity level of the α-azoalkylcuprates is noteworthy. The amido ($RCuNEt_2Li$) and phenylthio (RCuSPhLi) reagents exhibited a sufficient level of reactivity without the need for activating agents (i.e., TMSCl) to give conjugate transfer of the α-azoalkyl ligands to α,β-enones. The propensity of RCuSPhLi to give conjugate transfer of the α-azoalkyl ligand to 2-cyclohexen-1-one in THF and Et_2O with comparable yields suggests that the reagent may not be very susceptible to solvent conditions which can encumber cuprate conjugate addition reactions [1,11,12]). The ability of ethyl crotonate to participate in the 1,4-addition reaction with RCuSPhLi in THF is impressive because enoates are known to be poor substrates in conjugate addition reactions with cuprates [1,13] and often require extensive modifications of the reaction conditions such as solvent modifications and the addition of activating agents (e.g., TMSI or TMSCl) in order to achieve any significant level of 1,4-addition [1,13,14]. Also, the fact that the alkylcopper reagents [(RCu · TMEDA + TMSCl and $RCu \cdot PBu_3$] gave effective conjugate transfer of the α-azoalkyl ligand is impressive because alkylcopper reagents are often less reactive than their homocuprate counterparts [1,15]. From the limited reactivity profile based on reaction yields, this suggests that the α-azoalkyl cuprate/copper reagents are of the same order of magnitude of reactivity as simple alkylcuprate/copper reagents despite the presence of an α-nitrogen.

Examination of the 1,4-addition adducts from the enones and enoates by ^1H and ^{13}C NMR spectroscopy revealed that there was a limited degree of diastereoselectivity (0–39%) (cf. Table 1). A variety of parameters could be influencing the diastereochemical outcome such as reagent type, solvent, reaction temperature, and additives.

The phenylthiocuprate (RCuSPhLi) derived from the PhNHN=CHEt (**7**) underwent 1,4-addition to 2-cyclohexen-1-one. This reaction was noteworthy because the ambident anions derived from phenyl hydrazones have been reported to participate in substitution reactions to give nitrogen alkylation instead of carbon alkylation [5]. In marked contrast, by using copper intermediates, the regioselectivity of ambident α-azoalkyl anions derived form phenyl hydrazones was controlled, giving access to carbon alkylation. This effect may be similar to the regioselective alkylation of copper dienolates reported by Katzenellenbogen and coworkers [16,17]. The reaction of the copper mediated phenylazoalkyl ligand transfer may involve similar effects in electronic density localization responsible for favoring C-alkylation over N-alkylation. However, the reaction may be limited and subject to choice of copper (I) salt as well as possible electronic effects of the phenyl hydrazone. This is based on the fact that the phenyl hydrazone of benzaldehyde failed to give 1,4-addition with the phenylthiocopper reagent and the cyanocuprate ($R_2CuCNLi_2$) reagent even in the presence of TMSCl. It is possible that the phenyl group may be altering the electron density giving preference for Cu–N interactions over Cu–C, thereby, preventing 1,4-addition by the formation of an unreactive copper reagent [$(PhC{=}N{-}NPh)_2CuCNLi_2$]. This is consistent with the observation that amides are non-transferable ligands on copper [1,18].

Transformation of the resulting azo adducts into synthetically useful γ-amino ketone or ester adducts was problematic. The cleavage of the azo functionality (R–N=N–R′) to *N*-alkyl amines is reported to be very difficult requiring harsh reaction conditions [5]. For the azo adducts derived from phenylhydrazones, milder conditions have been reported by Baldwin for the transformation of the phenyl azo adducts into free amine

derivatives. Using copper reagents derived from phenylhydrazones, the phenyl azo adducts resulting from 1,4-addition to α,β-unsaturated enones and enoates may be manipulated to give γ-amino functionalization. Even though the γ-amino carbonyl derivatives are not directly available, the ester adducts can be transformed into 1,3-dicarbonyl derivatives as demonstrated by Baldwin.

4. Summary

α-Azoalkyl cuprate/copper reagents successfully undergo conjugate addition reactions. The necessity of using sterically unhindered substrates and the inability to transform the resulting azo adducts into free amine derivatives limit the methodology. The α-azoalkyl copper/cuprate reagents partially alleviate the limitations encountered by Baldwin and expanded the number and types of substrates that will participate in 1,4-addition reactions with α-azoalkyl carbanions. Additionally, this work has expanded the area of α-heteroatomalkyl copper/cuprate chemistry wherein the heteroatom is nitrogen and has probed the potential ability of copper to control the regioselectivity in allylic anions with ambident carbanion and amide anion character.

5. Experimental section

NMR spectra were recorded as $CDCl_3$ solutions on a Bruker AC-300 instrument. The ^1H NMR (300.1 MHz) chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane ($\delta_{TMS} = 0.0$ ppm) as an internal standard. The ^{13}C NMR (75.4 MHz) chemical shifts are reported in ppm downfield from TMS and referenced with respect to the $CDCl_3$ signal ($\delta_{CDCl_3} = 77.0$ for the center line). Infrared spectra were recorded on a Nicolet 5 DX FT-IR spectrometer as liquid films on sodium chloride plates unless otherwise noted. Mass spectral measurements were performed on a Hewlett-Packard 5840 or 5890 gas chromatograph/mass spectrometer at 70 eV and mass data are tabulated as m/z and intensity is expressed as percent of the base peak. Elemental analyses were determined by Atlantic Microlab Inc., Norcross, GA, USA.

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and *N,N,N',N'*-tetramethylethylenediamine were distilled from CaH_2. Chlorotrimethylsilane was distilled from CaH_2 or 4 Å molecular sieves. CuCN was used without purification (if necessary, it was dried under high vacuum (≈ 0.005 mmHg) with heat (90–100 °C) with stirring.) CuI was purified by the method of House [19] and stored in the dark. CuSPh was either purchased from Aldrich or prepared by the method of Adams and co-workers [20]. ^{n}BuLi (2.5 M in hexane) was purchased from Aldrich Chemical Co. and titrated regularly by the method of Shapiro and co-workers [21].

Column chromatography was performed using standard techniques employing silica gel (60–200 mesh). Radial chromatography was performed on a Chromatotron® apparatus using silica gel (EM Science, Kieselgel 60 PF_{254} Gipshaltig) coated rotorary TLC plates (2 mm thickness). Analytical TLC was performed with silica gel (60 F_{254}) coated aluminum backed plates (0.2 mm thickness). Preparative TLC was performed using silica gel coated glass plates with a 1 mm thickness of silica gel-GF purchased from Analtech Inc. Visualization of compounds on the analytical TLC plates was achieved by UV (254 nm) or in combination with staining solutions (4% phosphomolybdic acid in EtOH, or 0.5% 2,4-dinitrophenyl hydrazine in a 2 M aq HCl–EtOH solution.)

All glassware was flame-dried and cooled under a dry nitrogen atmosphere. All cuprate reactions were conducted under a positive, dry nitrogen–argon atmosphere in anhydrous solvents in round bottomed flasks fitted with new, clean rubber septa secured with Parafilm®. Flask to flask transfer of air and moisture sensitive intermediates was completed using double-tipped needles (cannula) under a positive argon pressure maintained by double layered balloons filled with argon. Low temperature baths (−78 °C or warmer) were prepared using shallow dewars with a Neslab CC-60 II or CC-80 II cyrocool machine, liquid nitrogen–isopropyl alcohol mixture or a dry ice–acetone slurry.

5.1. 3-(1-tert-Butylazo-ethyl)-cyclohexanone (2); (Table 1, entry 1)

(RCuSPhLi in THF) [7]: to tert-butyl hydrazone 1 (0.229 g, 2 mmol) in THF (4 mL) at −25– − 30 °C was added ^{n}BuLi (0.8 ml, 2 mmol) followed by stirring for 57 min to give a yellow solution. This solution was transferred by cannula to CuSPh (0.345 g, 2 mmol) suspended in THF (3 ml) at −25– − 30 °C. The resulting mixture (homogenous) was stirred for 23 min and then cooled to −78 °C followed by addition of 2-cyclohexen-1-one (0.17 ml, 1.75 mmol) via syringe. The reaction mixture was allowed to stir at −78 °C for 1 h and then allowed to warm slowly to room temperature over 8 h. The reaction was quenched with MeOH (1 ml) followed by the addition of saturated aqueous NH_4Cl and Et_2O. This mixture was filtered by vacuum through Celite. The aqueous phase was extracted 3 times with Et_2O and the combined extracts were washed with saturated aqueous NH_4Cl and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo afforded the crude material (0.227 g, 61% recovery of clean product as determined by ^1H NMR) which was purified using radial chromatography (silica gel) eluting with 20% EtOAc–80% petroleum ether mixture to give

pure **2** as a liquid (0.077 g, 33% yield): IR 2973 (s), 1714 (s), 1474 (m), 1451 (s), 1361 (s), 1315 (m), 1252 (m), 1225 (s), 1119 (w), 1062 (w), 900 (w); ^{1}H NMR δ 1.14 [(1.16, diastereomer), d, $J = 4.8$ Hz, 3 H] 1.19, [(1.20, diastereomer), s, 9 H], 1.31–1.49 (br m, 1 H), 1.56–1.75 (br m, 1 H), 1.78–2.55 (br m, 7 H), 3.22–3.32 (m, 1 H); ^{13}C NMR δ 15.7 (16.2, diasteromer), 24.9 (25.0, diastereomer), 26.7 (3 C); 27.4 (28.0, diastereomer), 41.3 (41.4, diastereomer), 42.8 (42.9, diastereomer), 44.3 (44.5, diastereomer), 66.9, 75.7 (75.8, diastereomer), 211.1; mass spectrum *m/z* (intensity) EI 211 (0.1, M + 1), 115 (1.1, M–CH(CH$_3$)N=N^{t}Bu), 57 (100, ^{t}Bu$^+$); CI 212 (15.3, M + 2), 211 (100, M + 1). Anal. Calc. for $C_{12}H_{22}N_2O$: C, 68.57; H, 10.47. Found C, 68.62; H, 10.55.

(Table 1, entry 3) (RCuNEt$_2$Li): to the tert-butyl hydrazone **1** (0.115 g, 1.0 mmol) in THF (2 ml) at 0 °C was added ^{n}BuLi (0.45 ml, 1.0 mmol) and the solution was stirred for 1 h. To CuI (0.194 g, 1.0 mmol at −20– − 30 °C was added LiNEt$_2$ [diethylamine (0.10 ml, 1.0 mmol) + ^{n}BuLi (0.45 ml, 1.0 mmol), 0 °C, 1 ml THF, 11 min] and this mixture was stirred for 25 min (olive-green suspension). To the CuNEt$_2$ mixture was added the hydrazone anion solution by cannular transfer plus a 1 ml THF rinse of the flask containing the hydrazone anion. The resulting mixture was stirred for 34 min (brown-yellow, turbid solution) and then cooled to −78 °C. 2-Cyclohexen-1-one (0.09 ml, 0.95 mmol) was added by syringe and the reaction mixture was stirred for 33 min, then put in a 0 °C bath for 15 min, and then quenched with saturated NH_4Cl (aq). The reaction mixture was diluted with Et_2O, washed with saturated NH_4Cl, brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded crude **2** (0.166 g) which was purified using radial chromatography (silica gel) eluting with 50% Et_2O–50% petroleum ether (v/v) mixture to give pure **2** as a liquid (0.085 g, 42% yield).

5.2. 3-(1-tert-Butylazo-ethyl)-cyclopentanone (3); (Table 1, entry 7)

(RCu · TMEDA + TMSCl) [2a,9]: to the tert-butyl hydrazone **1** (0.175 g, 1.5 mmol) in THF (3 ml) at 0 °C was added ^{n}BuLi (0.73 ml, 1.5 mmol) and the solution was stirred for 1 h. To CuI (0.289 g, 1.5 mmol in THF (3 ml) at room temperature was added dropwise by syringe TMEDA (0.68 ml, 4.5 mmol) and this mixture was stirred for 28 min, affording a white to pale violet cloudy solution. The CuI–TMEDA mixture was cooled to −78 °C and the lithiated hydrazone solution was added by cannular transfer plus a 1 ml THF rinse of the hydrazone anion pot. The resulting mixture was stirred for 28 min giving a brown-yellow suspension. TMSCl (0.47 ml, 3.7 mmol) was added dropwise by syringe and the reaction mixture was allowed to stir for 2 min. To this resulting mixture was added 2-cyclopenten-1-one (0.08 ml, 0.95 mmol) in THF (1.5 ml) by syringe. The reaction was allowed to stir for 1 h at −78 °C, then at 0 °C for 0.5 h and quenched by the addition of H_2O (1 ml). This mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl followed by brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo afforded the crude material (0.310 g) as a mixture of the ketone and trimethylsilyl enol ether 1,4-adducts as determined by ^{1}H NMR analysis. Upon standing the trimethylsilyl enol ether slowly hydrolyzed. Filtration of the crude material through a short plug of alumina (EtOAc–petroleum ether) afforded crude 3 (0.158 g, 85%, clean as determined by ^{1}H NMR analysis) which was purified using radial chromatography (silica gel) eluting with 50% Et_2O– 50% petroleum ether (v/v) mixture to give pure **3** as a liquid (0.115 g, 61% yield): IR 2974 (s), 2930 (s), 2897 (s), 1744 (s), 1475 (m), 1457 (m), 1406 (m), 1362 (s), 1211 (m), 1160 (m), 1126 (w), 901 (w); ^{1}H NMR δ 1.17–1.25 (m, 12 H), 1.53–1.67 (m, 1 H), 1.89–2.05 (m, 2 H), 2.09–2.46 (m, 3 H), 2.58–2.76 (m, 1 H), 3.31–3.40 (m, 1 H); ^{13}C NMR δ 16.8 (17.2, diastereomer), 26.0 (26.4, diastereomer), 26.7 (3 C), 38.2, 41.1, 41.9, 66.8, 76.2, 218.49 (218.7, diastereomer). Anal. Calc. for $C_{11}H_{20}N_2O$: C, 67.36; H, 10.19. Found C, 66.86; H, 10.31.

5.3. 4-tert-Butylazo-3-methyl-pentanoic acid ethyl ester (4); (Table 1, entry 8)

(RCuSPhLi in THF): to tert-butyl hydrazone 1 (0.233 g, 2 mmol) in THF (3 ml) at −25– − 30 °C was added ^{n}BuLi (0.91 ml, 2 mmol) and this solution was stirred for 15 min. This solution was transferred by cannula to CuSPh (0.3466 g, 2 mmol) suspended in THF (4 ml) at −25– − 30 °C. The resulting mixture was stirred for 15 min, affording a homogenous amber colored solution and then cooled to −78 °C followed by the addition of ethyl crotonate (0.22 ml, 1.8 mmol) by syringe. The reaction mixture was allowed to warm slowly to room temperature over 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. This mixture was filtered by aid of vacuum through Celite with a generous Et_2O–H_2O rinse. The mixture was extracted with Et_2O (3 times) and the combined extracts were washed with saturated aqueous NH_4Cl followed by brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude material (0.338 g, 88% recovery of clean product as determined by ^{1}H NMR) which was purified using radial chromatography (silica gel) eluting with 20% Et_2O–80% petroleum ether (v/v) mixture to give pure **4** as a liquid (0.177 g, 43% yield): IR 2973 (s), 1735 (s), 1454 (m), 1337 (m), 1363 (m), 1273 (m), 1250 (m), 1182 (m), 1098 (w) 1033 (m); ^{1}H NMR δ 0.99 (d, $J = 6.9$ Hz, 3 H), 1.13 (d, $J = 6.9$ Hz,

3 H), 1.18 (s, 9 H), 1.25 (t, $J = 7.2$ Hz, 3 H), 2.07–2.15 (m, 1 H), 2.35–2.53 (m, 2 H), 3.18–3.33 (m, 1 H), 4.13 (q, $J = 7.2$ Hz, 2 H); ^{13}C NMR δ 14.1, 15.5 (15.7 diastereomer), 15.8 (16.4 diastereomer), 26.7 (3 C), 34.4, 37.9 (38.2 diastereomer), 60.1, 66.7, 75.3 (75.8 diastereomer), 172.8 (173.0 diastereomer). Anal. Calc. for $C_{12}H_{24}N_2O_2$: C, 63.18; H, 10.52. Found C, 62.96; H, 10.55.

5.4. 2-(2-tert-butylazo-1-methyl-propyl)-malonic acid diethyl ester (5); (Table 1, entry 9)

(RCuSPhLi in THF): to tert-butyl hydrazone **1** (0.114 g, 1 mmol) in THF (2 ml) at −25– −30 °C was added ^{n}BuLi (0.53 ml, 1 mmol) and this solution was stirred for 15 min. This solution was transferred by cannula to CuSPh (0.170 g, 1 mmol) suspended in THF (3 ml) at −25– −30 °C. The resulting mixture was stirred for 15 min, affording a homogenous amber colored solution and then cooled to −78 °C followed by the addition of 2-ethylidene diethyl malonate [22] (0.164 g, 0.88 mmol) by syringe. The reaction mixture was allowed to warm slowly to room temperature over 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. This mixture was filtered by aid of vacuum through Celite with a generous Et_2O–H_2O rinse. The mixture was extracted with Et_2O (three times) and the combined extracts were washed with saturated aqueous NH_4Cl followed by brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude material (0.222 g, 84% recovery of clean product as determined by ^{1}H NMR) which was purified using preparative TLC (silica gel) eluting with 10% Et_2O–90% petroleum ether (v/v) mixture to give pure **5** as a liquid (0.081 g, 31% yield): ^{1}H NMR δ 0.97–1.30 (m, 12 H), 1.25 (s, 9 H), 2.64–2.83 (m, 1 H), 3.34–3.49 (m, 2 H), 4.10–4.25 (m, 4 H); ^{13}C NMR δ 12.4 (12.9 diastereomer), 14.0, 15.7 (16.5 diastereomer), 26.7 (3 C), 37.4 (37.7 diastereomer), 53.5 (55.0 diastereomer), 60.9 (61.2 diastereomer), 67.1, 72.5 (73.5 diastereomer), 168.3 (168.5 diastereomer), 168.6 (169.1 diastereomer). Anal. Calc. for $C_{15}H_{28}N_2O_4$: C, 59.98; H, 9.39. Found C, 59.72; H, 9.33.

5.5. 3-(1-Phenylazo-propyl)-cyclohexanone (9); (Scheme 3)

(RCuSPhLi in THF): to the phenyl hydrazone 6 (0.299 g, 2 mmol) in THF (3 ml) at −20– −25 °C was added ^{n}BuLi (0.91 ml, 2 mmol) and the mixture was stirred for 15 min. This resulting solution was transferred by cannula to CuSPh (0.343 g, 2 mmol) suspended in THF (4 ml) at −20– −25 °C plus an additional THF (1 ml) rinse of the hydrazone anion pot. The resulting mixture was stirred for 15 min to give a homogenous, golden colored solution and then was cooled to −78 °C followed by the addition of 2-cyclohexen-1-one (0.17 ml, 1.8 mmol) by syringe. The reaction mixture was allowed to stir at −78 °C for 80 min and then allowed to slowly warm to room temperature over 5 h. The reaction was quenched by the addition of H_2O. This mixture was filtered by vacuum through Celite with generous amounts of Et_2O and H_2O rinses. The aqueous phase was extracted three times with Et_2O and the combined organic phase was washed with saturated aqueous NH_4Cl, 5% aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo afforded the crude **6** (0.386 g), which was purified using preparative TLC (silica gel, 2 mm thickness) eluting with a 20% ethyl acetate–80% petroleum ether mixture to give **6** (> 90% pure by NMR analysis) as an unstable reddish-orange oil (0.112 g, 46% yield): IR 3064 (s), 2966 (s), 2938 (s), 2875 (s), 1960 (w), 1890 (w), 1714 (s), 1595 (m), 1496 (m), 1454 (m), 1314 (m), 1229 (m), 765 (s), 695 (s); ^{1}H NMR δ 0.83 (t, $J = 7.4$ Hz, 3 H), 1.43–1.68 (m, 2 H), 1.75–2.57 (m, 2 H), 3.32–3.38 (m, 1 H), 7.27–7.50 (m, 3 H), 7.66–7.70 (m, 2 H); ^{13}C NMR δ 10.5, 23.5, 25.0, 27.4, 41.4, 41.9, 45.1, 82.8, 122.2 (2 C), 128.9 (2 C), 130.5, 151.7, 211.3.

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