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One-Pot Synthesis of Homoallylic Ketones from the Addition of Vinyl Grignard Reagent to Carboxylic Esters

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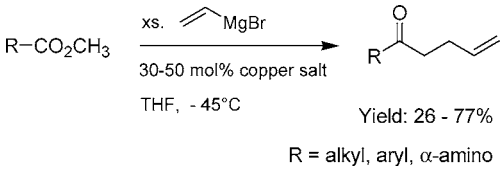
ABSTRACT



Fifteen homoallylic ketones have been synthesized in 26–77% yields on treatment of aromatic, aliphatic, and α-amino methyl carboxylates with excess vinylmagnesium bromide and catalytic amounts of a copper salt in THF. α-Amino homoallylic ketones derived from N-protected α-amino esters possessing aliphatic and alcohol side chains were synthesized in ≥98% enantiomeric purity.

The γ,δ-unsaturated carbonyl unit is often found in natural products.[1] Homoallylic ketones of this type have served as important versatile building blocks for the synthesis of pyrroles,[2] dihydropyrroles,[3] pyridines,[4] isoquinolines,[4a] cyclopropanes,[5] cyclopentyl derivatives,[6] cyclic peroxides,[7] 8-oxabicyclo[3.2.1]octanes,[8] bromopyranes,[9] and bishomoallyllithium reagents.[10] Furthermore, γ,δ-unsaturated ketones have been the topic of many physical organic studies involving their rearrangement under thermal,[11a] photochemical,[11b] and Lewis acid-induced conditions.[11c]

Several methods exist for the construction of the γ,δ-unsaturated carbonyl unit. For example, 1,4-addition of lithium vinyl cuprates,[12] organoboranes,[13] 2-benzotriazolyl-2-arylethylsilanes,[14] and α-zirconated vinylsilanes[15] to α,β-unsaturated compounds has given homoallylic ketones in good yield. Alternative protocols include the allylation of

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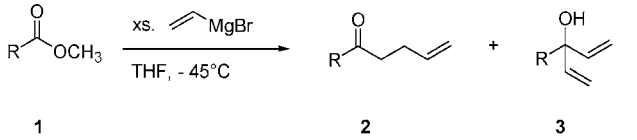
silyl enol ethers[16] and various allylations of unsaturated compounds under ruthenium,[17] palladium,[18] and copper catalysis.[19] The Claisen−Cope[20] and Carroll rearrangements[21] and Wittig[22] methodology have also found utility in the construction of γ,δ-unsaturated carbonyl compounds.

In our program aimed at β,β-dialkyl-substituted serine analogues,[23] the addition of excess vinylmagnesium bromide to *N*-(Boc)serine methyl ester **1j** at −78 °C in THF gave homoallylic ketone **2j** as a major side-product (Scheme 1 and Table 1), in addition to the expected tertiary alcohol **3j** (1:1 ratio). Formation of homoallylic ketone **2** was presumed to be due to collapse of the tetrahedral intermediate with expulsion of methoxide ion, followed by conjugate addition to the resulting enone (Scheme 2). This side reaction has not been widely discussed in the literature, though it has been previously observed during the addition of excess vinylmagnesium chloride to α-hydroxycarboxylic ester derivatives.[24] Moreover, the addition of vinylmagnesium bromide to amides has been shown to furnish β-aminoethyl ketones by

Scheme 1



Scheme 2

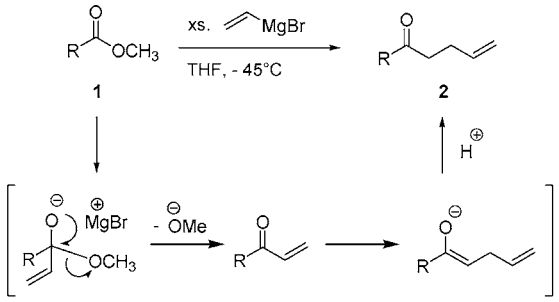
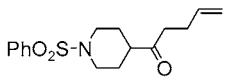
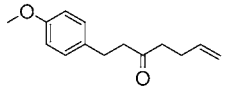
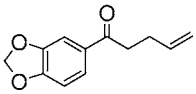
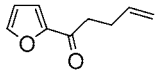
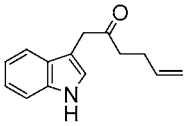
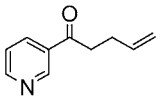
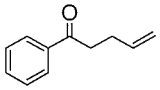
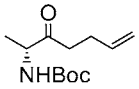
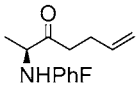
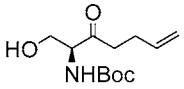
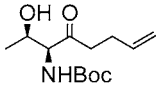
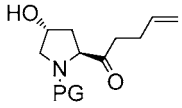
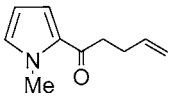
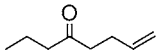


Table 1. Examples of Homoallylic Ketones **2** Obtained by Reaction of **1** with CH_2=CHMgBr (300−500 Mol %), $Cu(OAc)_2$ (30−50 Mol %) in THF at −45 °C

entry	product (**2**)	% isolated yield
a		55
b		64
c		51
d		48
e		37
f		42[a]
g		60[a]
h		77[b]
i		26[a,c,c]
j		59[b]
k		49
l m		(PG = Boc) 70[a] (PG = PhF) 70[a,c]
n		36[a]
o		29

[a] Reaction performed in absence of copper. [b] Reaction performed in the presence of 30−40 mol % CuCN. [c] PhF = *N*-(9-phenylfluoren-9-yl). [d] Starting material was recovered in 30% yield.

(16) (a) Mukaiyama, T.; Nagaoka, H.; Ohshima, M.; Murakami, M. *Chem. Lett.* **1986**, 1009−1012. (b) Kudo, K.; Saigo, K.; Hashimoto, Y.; Houchigai, H.; Hasegawa, M. *Tetrahedron Lett.* **1991**, *32*, 4311−4312. (c) Kudo, K.; Hashimoto, Y.; Houchigai, H.; Hasegawa, M.; Saigo, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 848−856.

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a sequential 1,2-addition of the vinyl Grignard reagent followed by 1,4-addition of the displaced amine onto the enone intermediate.[25] Conditions have now been developed to favor formation of homoallylic ketone **2** using a diverse set of carboxylic esters, the results of which are reported herein (Table 1).

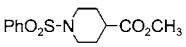
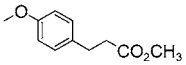
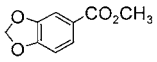
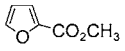
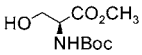
Reaction conditions were initially optimized using *N*-(Boc)serine methyl ester **1j** as a substrate. The yield of homoallylic ketone **2j** was augmented by the addition of copper salts.[26] For example, sequential addition of 10 mol % anhydrous $Cu(OAc)_2$, followed by a THF solution of **1j** to the vinyl Grignard reagent (500 mol %) at −45 °C, gave a 4:1 mixture of **2j**:**3j** as determined by ^{1}H NMR spectroscopy of the crude product. Although this ratio could be improved by increasing the proportion of $Cu(OAc)_2$ (>99:1 with 100 mol %), ketone **2j** was typically accompanied by increased amounts of unreacted starting material (**1j**:**2j** = 30:70). Substitution of $Cu(OAc)_2$ with $Cu(OAc)_2 \cdot H_2O$ and with CuCN (30−50 mol %) gave equally successful results using commercial and freshly prepared Grignard reagent.

With appropriate conditions in hand,[27] a variety of methyl esters were examined in this reaction (Table 1). Aliphatic, aromatic, and α-amino methyl esters all furnished the respective homoallylic ketone **2** in moderate to good yields, demonstrating that the reaction conditions were tolerant of a wide variety of functional groups. Reactions were successfully performed on a 1−13 mmol scale.

When tertiary alcohol formation was significant (25−50%) with Grignard reagent alone, the addition of copper salts generally promoted higher ketone:alcohol ratios (Table 2). In the absence of copper, sterically encumbered substrates (Table 1, entries i, l, and m) gave **2** contaminated with ≤5% tertiary alcohol, as shown by ^{1}H NMR analysis; however, complete reaction required generally several days at room temperature.[28]

Although TLC analysis of crude product on silica gel always showed baseline material, ^{1}H NMR spectroscopic examination of crude product after extractive workup often revealed clean spectra with little evidence of unreacted starting material. Chromatographic purification was facilitated by the fact that ketone **2** always eluted faster than alcohol **3**; nonetheless, typical isolated yields of ketone **2** were inconsistent with the spectroscopic observations, suggesting that poor mass recovery may be due to purification. Exposure of compound **2g** to a slurry of silica gel and the appropriate chromatography solvent did not provide evidence of decomposition after several days; however, limited success was achieved with different workup procedures and chromatography absorbents (silica gel, alumina, florisil). Silica gel chromatography of crude **2g** (observed by ^{1}H NMR spectroscopy as a 90:10 mixture of **2g**:**3g**) resulted typically in 40−55% isolated yields. Alternatively, distillation of the crude mixture followed by chromatography over basic alumina to remove **3g** gave an improved yield of **2g** (60%, Table 1). Thus, the yields given in Table 1 may be improved by further optimization of the catalytic conditions and purification procedure.

Table 2. Influence of Added Copper Salts on the Ratio of **2**:**3**[a]

Entry	substrate **1**	ratio **2**:**3**[b]	ratio **2**:**3**[c]	% conversion[c]
1		75:25	≥ 95 : 5[d]	≥ 95
2		75:25	≥ 95 : 5[e]	≥ 95
3		75:25	85 : 15[f]	≥ 98
4		75:25	≥ 95 : 5[d]	≥ 98
5		50:50	92 : 8[f]	≥ 98

[a] As determined by ^{1}H NMR spectroscopy. [b] In absence of copper catalyst. [c] In presence of copper catalyst. [d] Performed with 50 mol % $Cu(OAc)_2$. [e] Performed with 30 mol % $Cu(OAc)_2$. [f] Performed with 30 mol % CuCN.

α-Amino ketones[29] are useful precursors in the synthesis of natural products and biologically active substances. α-Amino homoallylic ketones have been previously synthesized from *N*-(Boc)-α-amino acids in 75−92% yields by preactivation of the carboxylate as *N*,*O*-dimethyl hydroxamates[30a] and *S*-pyridinyl esters;[30b,c] however, the enantio-

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(27) A solution of vinylmagnesium bromide in THF (1 M, 8.4 mL, 8.4 mmol) was cooled to −45 °C (dry ice/acetonitrile). Solid $Cu(OAc)_2$ (113.4 mg, 0.63 mmol) was added in one portion and the slurry stirred for 10 min. Ester **1b** (408 mg, 2.1 mmol) was then added dropwise. After 1 h, the reaction mixture was warmed to 0 °C, stirred for 1 h, and then brought to room temperature with overnight stirring. Workup and purification procedures and characterization data for **2b** are presented in Supporting Information.

(28) Steric crowding promotes 1,4-addition over 1,2-addition of Grignard reagents to enones. Cluzeau, J.; Lubell, W. D. *Israel J. Chem.* **2001**, *41*, 271−281 and references therein.

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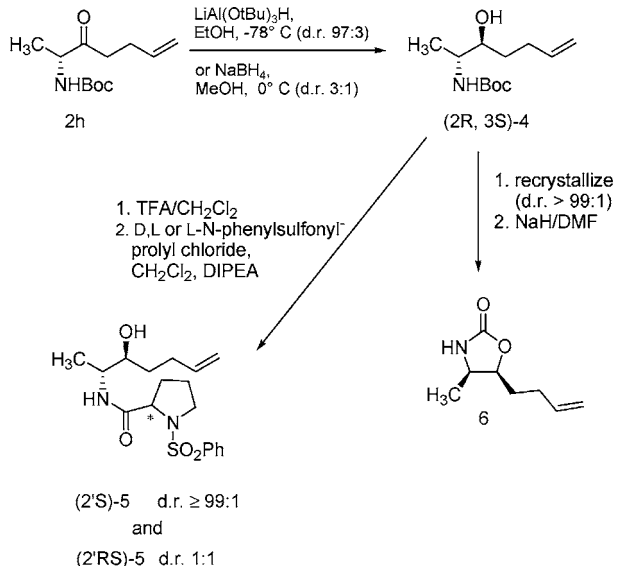
Scheme 3



meric purity of the ketone products was not addressed. Both the $Cu(acac)_2$-catalyzed 2,3-sigmatropic rearrangement of allyl sulfonium ylides[31a] and the desulfonation of α-alkylated γ-amino-β-ketosulfones[31b] were reported to furnish enantiopure α-amino homoallyl ketones. The acylation of the lithio dianion of methyl hippurate with 4-pentenoyl chloride also provided entry into α-amino homoallyl ketones,[32] albeit in racemic form. Because multiple steps and expensive reagents are often necessary for producing α-amino homoallyl ketones by these sequences, we investigated the addition of vinylmagnesium bromide to a series of N-protected α-amino esters **1h**−**m**. ^{1}H NMR spectroscopic examination of products **2k**−**m** did not show evidence of α-epimerization, as judged by the absence of diastereomeric signals. The enantiomeric purity of α-amino homoallyl ketone was ascertained by conversion of *N*-(Boc)alanine-derived ketone **2h** to amido alcohols **4** (Scheme 3). Ketone **2h** was reduced, respectively, with $LiAl(OtBu)_3H$[33] and $NaBH_4$ to provide 97:3 and 3:1 diastereomeric mixtures of alcohols **4** (major diastereomer shown).[34] Deprotection of the 3:1 mixture with TFA in CH_2Cl_2, followed by acylation with D,L-*N*-benzenesulfonylprolyl chloride,[29a] gave a 3:3:1:1 mixture of diastereomeric amido alcohols **5**, displaying distinct methyl doublets in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) at 1.13, 1.15, 1.19, and 1.22 ppm, respectively. By analogy, coupling of L-*N*-benzenesulfonylprolyl chloride[29a] to the diastereomeric mixture **4** provided product (2′*S*)-**5** in which no ^{1}H NMR signals for the upfield methyl doublet (δ 1.13) were observed. Incremental additions of (2′*RS*)-**5** to (2′*S*)-**5** demonstrated that diastereomeric ^{1}H NMR signals were detectable at levels of ∼1%. Hence, the enantiomeric purity of amino ketone **2h** is presumed to be ≥98%. Considering the effectiveness of alternative protecting groups (SO_2Ph and PhF), and the potential of ionizable side chain substituents to prevent α-epimerization on reaction with organometallic reagent due to polyanion formation,[29f] compounds **2i** and **2j** are also presumed to be enantiopure. This result demonstrates that minimal epimerization at the α-center occurs and that α-amino homoallyl ketones **2h**−**m** can be synthesized in high enantiomeric purity.

Fifteen homoallylic ketones have been synthesized in 26−77% yields on treatment of methyl carboxylates **1** with excess vinylmagnesium bromide and catalytic amounts of copper salts in THF. Our straightforward method for making γ,δ-unsaturated ketones offers a practical alternative for the synthesis of these versatile building blocks.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) Diastereomers **4** were inseparable by column chromatography but could be separated (≥99:1) by crystallization from hexane. The anti configuration of the major diastereomer (2*R*,3*S*)-**4** was assigned by analogy (see ref 33) and confirmed by examination of the ^{1}H NMR NOESY spectrum of oxazalidinone **6** in $CDCl_3$ solution.