mechanistic studies, there have been no measurements of secondary KIE for this prototypical five-membered ring intramolecular elimination reaction. Pyrolysis of trans-deuterated *(2R,3R)*-**3** (X = D) at 120 °C *afforded (+)*-apopinene (**2**) that had $[\alpha]_f = +1.343°$, and a secondary KIE of 1.061 may be calculated from the relationship[3] $k_H/k_D = ([\alpha]_i - [\alpha]_f)/([\alpha]_i + [\alpha]_f)$ where $[\alpha]_i = -45.1°$ (Table I). No discernable loss of deuterium was observed by mass spectral analysis confirming the syn elimination pathway. In a duplicate experiment, the recovered (+)-(*S*)-apopinene exhibited a rotation of $[\alpha]_D = +1.323°$ and a secondary KIE of 1.060. Thus, the perturbations of the bending vibrations of the C-H bonds at C_β in the elimination process are significant at the transition state (TS) as evidenced by the appreciable secondary KIE.

Pyrolysis of the cis-deuterated amine oxide **3** (Y = D) afforded apopinene with an optical rotation of +17.1°. Since the initial rotation of the (–)-(*R*)-apopinene used in the synthesis of **3** was –45.1°, the primary syn KIE for the concerted Cope elimination is found to be 2.22. A temperature correction to 25 °C suggests a primary KIE of ~2.8. An accompanying mass spectral analysis using selective ion monitoring (SIMS) on this same cis-deuterated amine oxide showed that the recovered alkene contained 69.0% of its original deuterium content and a k_H/k_D of 2.23 may be calculated from this datum. These combined data, *for a rate-limiting nonlinear hydrogen transfer with discernible rehybridization at* C_β, are consistent with a transition state with extensive double-bond character.

Since the oxygen of an amine oxide is weakly basic and a relatively late TS should be anticipated, it is instructive to use a stronger base in order to assess the relative magnitudes of the secondary KIE in a comparable elimination process. Mass spectral analysis of the apopinene recovered from the trans-deuterated quaternary ammonium iodide **4** (X = D) showed no detectable loss of deuterium upon elimination with potassium *tert*-butoxide in DMSO solvent. This process is therefore a 100% syn 1,2-elimination under these reaction conditions reflecting the association of the alkoxide base with the cationic ammonium center.[8] Treatment of trans-deuterated (2*R*,3*R*)-**4** (X = D) at 26 °C under these conditions afforded (+)-**2** that had $[\alpha]_f$ 1.54° and a secondary KIE of 1.072. The magnitude of this KIE is smaller than that of the Cope elimination when corrected to 25 °C (~1.05). The primary KIE of 1.27 (Table I) is also very small suggesting a somewhat earlier transition state when KO-*t*-Bu is employed in DMSO solvent where the potassium cation is highly coordinated and the base strength of the oxyanion is markedly increased.

In summary, we have described a highly sensitive method for measuring both primary and secondary KIE in elimination reactions.[9] These data provide the first experimental evidence for extensive rehybridization at carbon in the Cope elimination. Recent ab initio calculations[10] (MP2/631G*) of secondary KIE in the Cope elimination suggests that the rehybridization at C_α (secondary KIE = 1.11) is even geater than that at C_β (secondary KIE = 1.04). *These combined data provide a unique explanation for the* fact that a Cope elimination in the cyclooctyl system (a late TS) affords exclusively *cis*-cyclooctene. However, much stronger bases that involve an earlier TS with much less double-bond character give predominantly the highly strained *trans*-cyclooctene despite the fact its ground-state energy is 9 kcal/mol higher in energy.[3]

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[5] (a) Schrieber, S. L.; Claus, R. E.; Regan, J. *Tetrahedron Lett.* **1982**, 3867. (b) Eschinazi, H. E.; Pines, J. *J. Org. Chem.* **1959**, *24*, 1369. (c) Stemke, J. E.; Bond, F. T. *Tetrahedron Lett.* **1975**, 1815. (d) Brown, H. C.; Wolfgang, R. H.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565. (e) Icke, R. N.; Wisegarver, B. B.; Alles, G. A. *Organic Synthesis*; Hornung, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 723.

[6] (a) Cram, D. J.; McCarty, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740. (b) Cope, A. C.; LeBel, N. A. *Ibid.* **1960**, *82*, 4656. (c) Saunders, W. H., Jr.; Cockerill, A. F. *Mechanism of Elimination Reactions*; Wiley-Interscience: New York, 1973.

[7] Wright, D. R.; Sims, L. B.; Fry, A. *J. Am. Chem. Soc.* **1983**, *105*, 3714.

[8] (a) Chiao, W.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2802. (b) Bach, R. D.; Knight, J. W. *Tetrahedron Lett.* **1979**, 3815.

[9] For an earlier intermolecular polarimetric differential method involving the reaction of a racemate made up of one labeled enantiomer, see: Bergson, G.; Matsson, O.; Sjoberg, S. *Chem Scr.* **1977**, *11*, 25.

[10] Bach, R. D.; Owensby, A. L.; Andrês, J. L.; Gonzalez, C.; Schlegel, H. B. *J. Am. Chem. Soc.* Submitted for publication.

Synthesis of 1,4-Dicarbonyl Compounds via the Conjugate Addition of a Masked Activated Ester, ROCH(CN)$_2$

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Summary: A new acyl anion equivalent for the preparation of masked activated esters, the protected hydroxymalonitrile **1**, readily undergoes conjugate addition to α,β-unsaturated carbonyl derivatives **2** to give the masked 1,4-dicarbonyl compounds **3** in good to high yields. 1,4-Dicarbonyl compounds **4**, in which one of the two carbonyl groups has a reactivity different from the other, can be prepared selectively from **3**.

1,4-Dicarbonyl compounds are starting materials and intermediates in many important natural product syntheses, and a number of methods for their syntheses have appeared.[1] One of the most common approaches is the conjugate addition of acyl anion **5** or its equivalent to α,β-unsaturated carbonyl compounds.[1] Since the sub-

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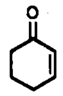
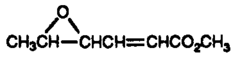
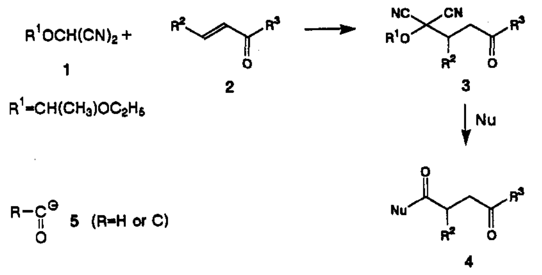
[1] For the syntheses of 1,4-dicarbonyl compounds via conjugate addition, see: Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 4926. Seyferth, D.; Hui, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4551. Shono, T.; Nishiguchi, I.; Ohmizu, H. *J. Am. Chem. Soc.* **1977**, *99*, 7396. Scheffold, R.; Orlinski, R. *J. Am. Chem. Soc.* **1983**, *105*, 7200. Mukaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8641. Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272. Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. Groebel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. Stetter, H. *Angew. Chem.* **1976**, *88*, 695. Krief, A. *Tetrahedron* **1980**, *36*, 2531.

Table I. Conjugate Addition Reactions of Protected Hydroxymalonitrile 1 with Electron-Deficient Olefins

entry	substrate	condns[a]	reaction time (h)	isolated yield of 3 (%)
1	$CH_2{=}CHCOCH_3$	A	9	76
2	$CH_2{=}CHCOCH_3$	B	12	85
3	$CH_2{=}CHCOCH_3$	C	24	71
4	$CH_3CH{=}CHCOCH_3$	A	12	86
5		A	12	82
6	$CH_2{=}CHCO_2CH_3$	A	10	90
7	$CH_3CH{=}CHCO_2CH_3$	A	12	87
8	$CH_3CH{=}CHCH{=}CHCO_2CH_3$	A	8	75
9	 $CH_3\overset{O}{CH{-}CH}CH{=}CHCO_2CH_3$	A[b]	18	86
10	$CH_2{=}CHCN$	A[b]	11	74

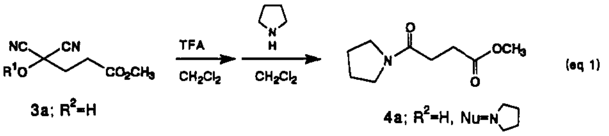
[a] Key: A, K_2CO_3 (1.1 equiv), 1 (1.2 equiv), acetone, rt; B, Et_3N (10 mol %), 1 (1.2 equiv), benzene, rt; C, $Ni(acac)_2$ (10 mol %), 1 (1.2 equiv), CH_3CN, 10 Kbar. [b] 1.5 equiv of 1 was used.

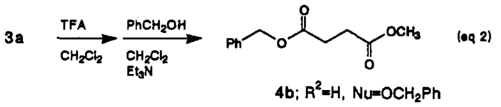
stituent R in 5 was hydrogen or carbon in the previous cases, the reactions which could be utilized for further manipulation of the γ-carbonyl group of the resulting 1,4-dicarbonyl adduct were limited to those of ketones and aldehydes. Moreover, the conjugate addition reactions are sometimes accompanied by 1,2-addition, and thus some optimization of the reaction conditions is often needed to minimize this side reaction.[2] We have recently developed a new acyl anion equivalent 1 for the preparation of masked activated esters.[3] If 1 undergoes efficient conjugate addition to 2, 1,4-dicarbonyl derivative 3 would be formed in which one of the two carbonyl groups can act as a masked activated ester equivalent, and thus further manipulation of the γ terminus would give 1,4-dicarbonyl compounds 4 which are not available by the previous methods.



The results are summarized in Table I. Three different types of conditions were examined for the reaction with methyl vinyl ketone. The use of K_2CO_3 (1.1 equiv) in acetone at room temperature or catalytic amounts of Et_3N (10 mol %) in benzene at room temperature gave the 1,4-adduct in good yields (entries 1 and 2). The 1,2-adduct was not produced at all. In addition to these weakly basic conditions, we examined the nickel-catalyzed procedure which was known as a mild and efficient option for carrying out Michael additions with β-dicarbonyl compounds.[4] Although the reaction with methyl vinyl ketone was very sluggish at 1 bar, the conjugate addition proceeded very smoothly at high pressures (e.g., 10 Kbar) (entry 3)[5] to give the same 1,4-adduct along with small amounts of the starting materials and no side reactions took place. Not only enones (entries 4 and 5) but also enoates underwent the conjugate addition (entries 6–9). The regioselectivity is noteworthy; neither 1,6-conjugate addition to the dienoate nor epoxide ring opening of the γ,δ-epoxy-α,β-enoate took place. The conjugate addition to acrylonitrile also proceeded very smoothly (entry 10).

Next we examined the unmasking conversion of 3 into 4. The ethoxyethyl group of 3a was removed with trifluoroacetic acid (TFA) in dichloromethane at 0 °C. After evaporation of TFA under reduced pressure at 0 °C, pyrrolidine was added to a dichloromethane solution of the resulting crude alcohol. Amide ester 4a was obtained in 88% yield (eq 1). The addition of benzyl alcohol and





triethylamine, instead of pyrrolidine, produced mixed ester 4b in 69% yield (eq 2). In conclusion, we are now in a position to prepare 1,4-dicarbonyl compounds which have different functional groups or different modifications of the same functional group via conjugate additions using 1 as a masked acyl anion.

The following procedure for the addition of 1 to methyl vinyl ketone is representative. To an anhydrous acetone solution (1.6 mL) of 1 (124 mg, 0.804 mmol) and methyl vinyl ketone (56 μL, 47 mg, 0.67 mmol) was added anhydrous K_2CO_3 (102 mg, 0.738 mmol), and the resulting heterogeneous mixture was stirred for 9 h at room temperature. Addition of saturated aqueous NH_4Cl solution, extraction with ether (three times), washing with saturated brine, drying ($MgSO_4$), concentration, and silica gel column chromatography with hexane–ethyl acetate (15:1) as eluant gave the adduct (115 mg, 0.513 mmol) in 76% yield.

Supplementary Material Available: Experimental details for the preparation of 3 and 4 and the spectral and analytical data of the products (4 pages). Ordering information is given on any current masthead page.

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(2) (a) Lucchett, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1979**, *29*, 2695. (b) Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100. (c) El-Bouz, M.; Wartski, L. *Tetrahedron Lett.* **1980**, *21*, 2897. Wartski, L.; El-Bouz, M. *Tetrahedron* **1982**, *38*, 3285.

(3) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515.

(4) Nelson, J. H.; Howells, P. N.; DeLullo, G. D.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246.

(5) For a recent example of high-pressure mediated organic reactions, see: Yamamoto, Y.; Furuta, T.; Kurata, T.; Matsuo, J. *J. Org. Chem.* **1991**, *56*, 5737 and references cited therein. See also: *Organic Synthesis at High Pressures*, Matsumoto, K., Acheson, R. M., Eds.; J. Wiley: New York, 1991.