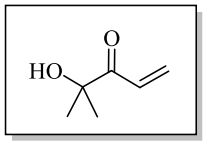
Palomo, C., Oiarbide, M. and García, J.M. (2019). 4-Hydroxy-4-methylpent-1-en-3-one. In Encyclopedia of Reagents for Organic Synthesis. https://doi.org/10.1002/047084289X.rn02220

4-Hydroxy-4-methylpent-1-en-3-one



[22082-43-5] • $C_6H_{10}O_2$ • (MW 114.14)

(electrophilic alkene used as an equivalent of acrylic acid and derived esters in Diels-Alder and 1,3-dipolar cycloaddition reactions, as well as conjugate addition reactions of carbon-centered nucleophiles; also used as a surrogate of acrolein and vinyl ketones.

Alternate Name(s): (1-hydroxy-1- methyl)ethyl vinyl ketone, 2-hydroxy-2-methylpent-4-en-3-one).

Physical Data: bp 45 °C (13 mmHg), n_D^{20} 1.4412.

Solubility: sol organics (CH_2Cl_2, toluene, THF). Reacts with alcohols.

Form Supplied in: does not apply (colorless liquid).

Analysis of Reagent Purity: NMR

Preparative Methods: (from acetone and 1-methoxypropadiene[1] from 3-hydroxy-3-methyl-2-butanone[2]).

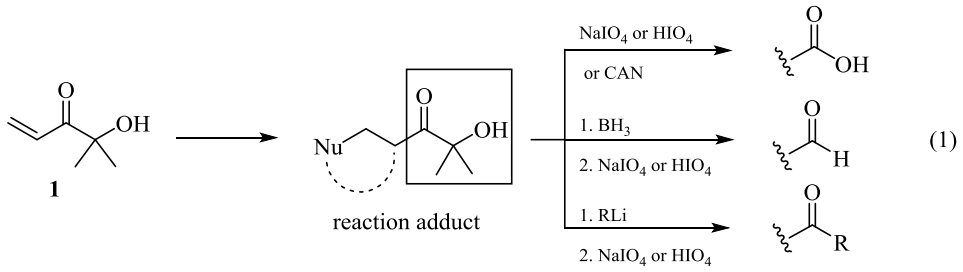
Purification: distillation under vacuum.

Handling, Storage, and Precautions: storage at –20 ºC under nitrogen.

Reagent **1** is an excellent a^3 synthon (acrylic acid equivalent) that participates as electrophilic partner in several categories of cycloaddition and conjugate addition reactions. While structurally related to simple enones, **1** has enhanced innate reactivity because of the intramolecular hydrogen-bond activation. Another difference with respect to simple enones is that **1** may reversibly form bidentate complexes with metal salts (primarily Cu(II), Mg(II) and Zn(II) species), and thus metal-catalyzed asymmetric

reactions involving **1** becomes feasible. Similarly, the reactivity and stereochemical biases of **1** can be tuned by some H-bond catalysts. This latter feature has allowed the development of efficient organocatalytic asymmetric methods based on reagent **1**.

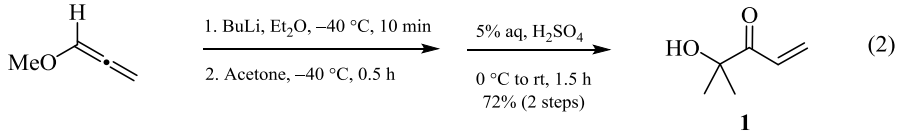
An additional feature of synthetic relevance is that the ketol moiety of adducts derived from **1** can be elaborated into: (i) carboxylic acids (by treatment with an oxidant such as $NaIO_4$, HIO_4 or cerium ammonium nitrate), (ii) aldehydes (treatment with borane and subsequent oxidation of the resulting diol) or (iii) ketones (addition of an alkyllithium and diol cleavage) (eq 1). The whole sequences above result environmentally friendly because the oxidative C–C scissions usually proceed in high yields and acetone is the only organic side product formed.[3]



(1)

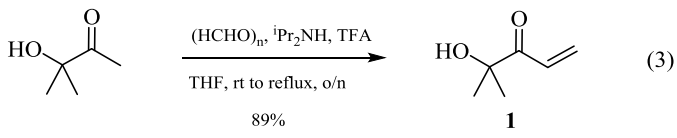
Synthesis

Reagent **1** has been prepared by addition of the lithium salt of 1-methoxypropadiene to acetone, followed by acidic hydrolysis of the resulting enol ether[1] (eq 2).



(2)

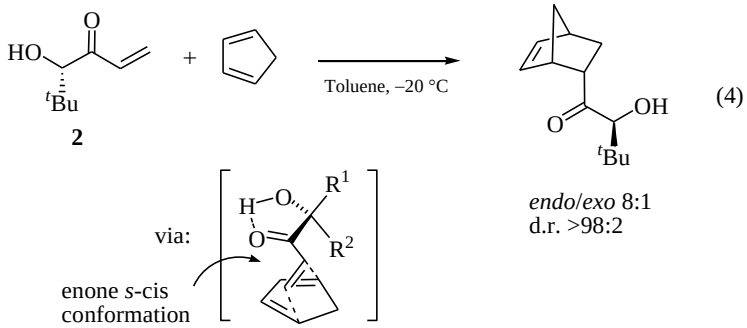
Alternatively, this reagent has been prepared in high yield by aldol condensation between commercial 3-hydroxy-3-methyl-2-butanone and paraformaldehyde[2] eq 3).



(3)

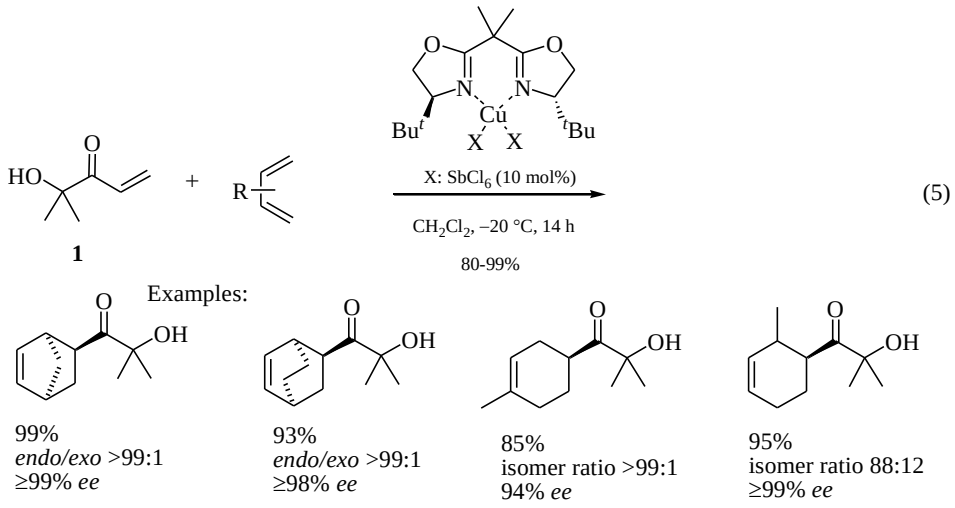
Cycloaddition reactions: Diels-Alder reaction

The internal chelation by hydrogen bond in **1** modulates its reactivity not only via electronic effects (LUMO lowering of dienophile), but also because of steric effects. As shown in eq 4, this chelation restricts the conformational freedom of the enone system, inducing it to adopt a *s-cis* conformation preferentially, because of destabilizing 1,3-allylic interactions predicted for the *s-trans* form. This combine effect was first demonstrated using chiral analogs of **1**, such as **2**, which reacts with cyclopentadiene to afford the corresponding Diels-Alder cycloadduct in good *endo*/*exo* selectivity and essentially perfect diastereoselectivity.[4]



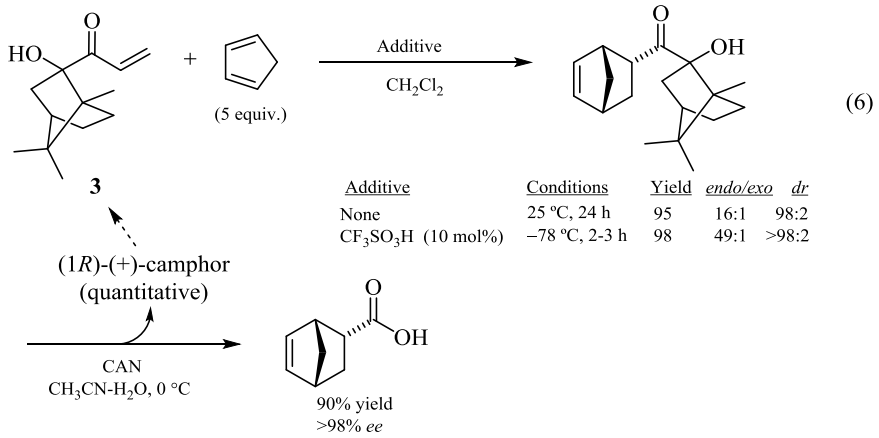
(4)

The ability of **1** to reversibly form 1,4-metal chelates has been translated to efficient asymmetric metal-catalyzed (typically Cu(bisoxazoline)$_2$-catalyzed) Diels-Alder reactions, which provide adducts in high regio-, diastereo-, and enantioselectivity even with less reactive dienes (eq 5).[5]



(5)

The Diels-Alder reactions of **1** can also be accelerated by addition of a protic acid such as triflic or trifluoroacetic acids. A highly stereoselective variant using the camphor-derived chiral analog of **1**, **3**, has been developed (eq 6).[6] The acid additive is believed to participate along with the ketol substrate in a cooperative H-bond network. One advantage of the chiral analog **3** over **2** is that camphor, the source of chiral information in the former case, is recovered after performing the ketol-to-carboxylic acid scission and can be recycled (eq 6).



Additive	Conditions	Yield	*endo/exo*	*dr*
None	25 °C, 24 h	95	16:1	98:2
CF_3SO_3H (10 mol%)	−78 °C, 2-3 h	98	49:1	>98:2

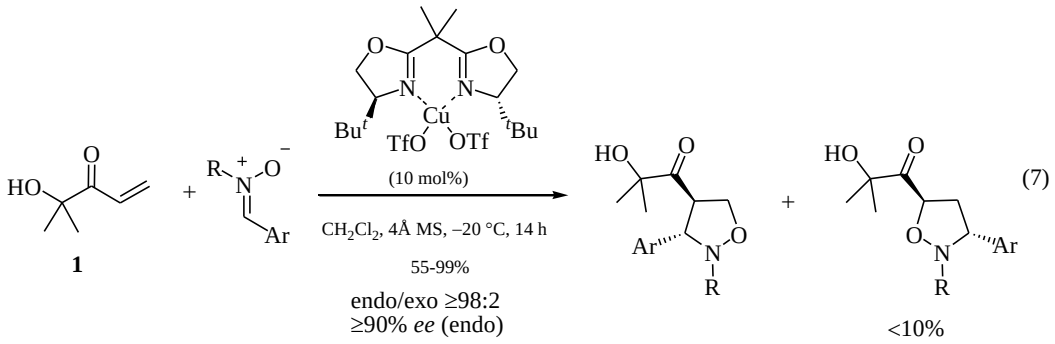
(6)

Both variants, namely metal-catalyzed and Brønsted acid-catalyzed, Diels-Alder reactions can also be performed successfully with analogs of reagent **1** bearing a substituent (either aliphatic or aromatic) of variable length/functionality at the β-carbon.[7] The method has been demonstrated to be superior to other conventional approaches in the total synthesis of the natural product (+)-cyanthiwigin U.[8]

Cycloaddition reactions: 1,3-dipolar reactions

Reagent **1** participates successfully as dipolarophile in asymmetric, catalytic 1,3-dipolar cycloadditions with nitrones, leading to the corresponding isoxazolidines (eq 7).[9] These types of cycloadditions have attracted considerable interest owing to the relevance of the resulting heterocycles, but also because of the challenging issues of stereoselectivity and

regioselectivity. Another common concern is catalyst deactivation by the strongly coordinating nitrone substrate. Reagent **1** works optimal in terms of reactivity and stereoselectivity in the presence of bis(oxazoline)-Cu(II) type catalysts and, importantly, the undesired regioisomeric products are formed in isolated yields lower than 10% (eq 7). It is worth to mention that oxidative cleavage of the ketol moiety in the resulting cycloadducts using the conditions mentioned above demonstrated to be perfectly compatible with the newly formed isoxazolidine ring. This cycloaddition reaction is equally effective with β-substituted analogs of **1** giving rise to trisubstituted isoxazolidines in an essentially enantiopure form.



Ar: Ph, 4-MeOPh, 4-MePh, 3-Me-4-MePh

R: Bn, Me

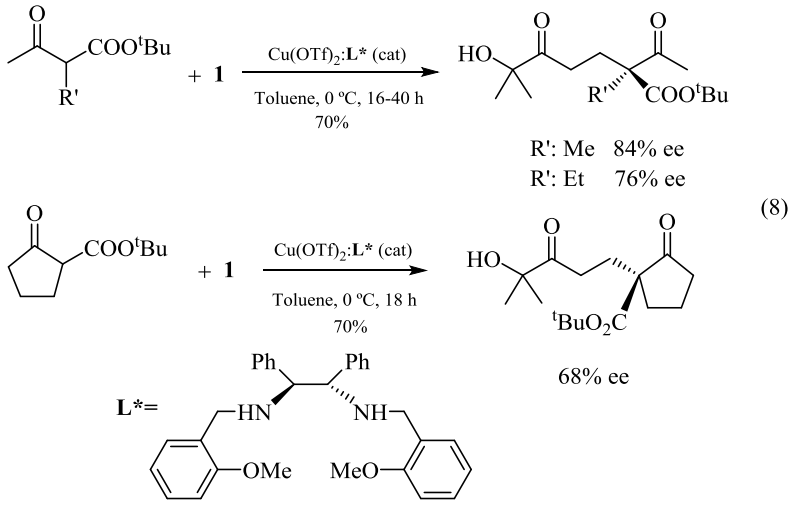
Conjugate addition reactions

Reagent **1** is amenable to react with several types of nucleophiles to yield the corresponding Michael addition products. As described above for the cycloaddition reactions, coordination of **1** to either a metal catalyst or a H-bond organocatalyst serves to accelerate the addition reaction and render it enantioselective by using the appropriate chiral catalyst. In many of these developments, control experiments carried out using common α,β-unsaturated carboxylic acid derivatives have demonstrated the superior behavior of **1**. Among the suitable combinations of substrates and reagents, both chiral

variants of **1** (addition of β-ketoesters[10a] and nitroalkanes[10b]) and α-[11] and β-substituted (Friedel-Crafts reactions,[12a,b] conjugate additions of dialkylzincs,[12c] carbamates,[12d] nitromethane,[12e] N,N-dialkyl hydrazones[12f] and radical additions[12g]) analogs of **1** have also been used.

Metal-catalyzed conjugated additions

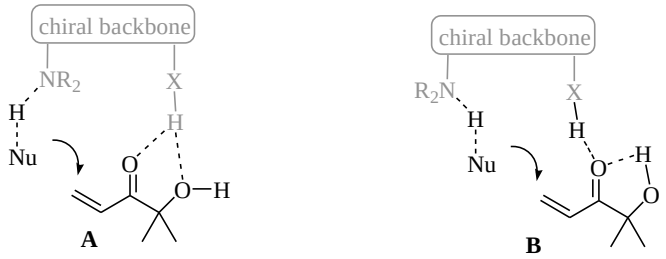
Hydroxy enone **1** acts as an efficient acrylic acid equivalent in the conjugate addition of acyclic and cyclic α-substituted β-ketoesters triggered by appropriate metal catalysts. In the presence of $Cu(OTf)_2$ and a *C*2-symmetric diamine ligand, the corresponding adducts are obtained with high yield and enantioselectivities from moderate to good[10a] (eq 8).



(8)

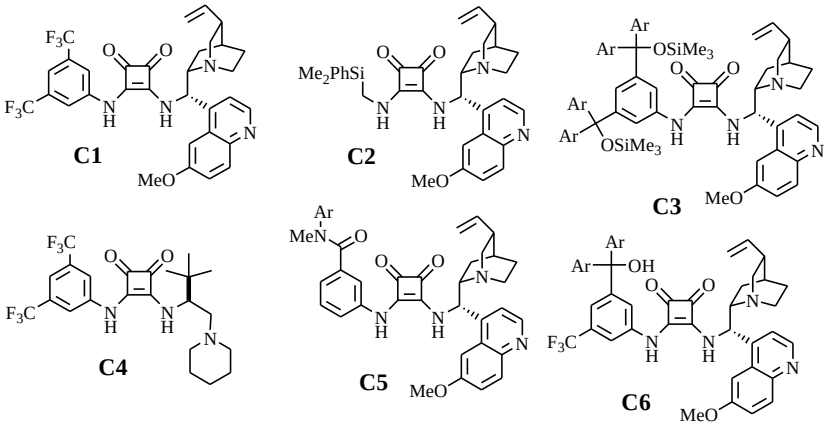
Brønsted base-catalyzed conjugated additions

Enantioselective conjugate addition reactions of pronucleophiles NuH to **1** can be promoted by bifunctional Brønsted base/H-bond catalysts. The catalyst, once gets protonated to deliver active species Nu^-, may engage in substrate activation via different H-bond networks, as in models **A** and **B** (eq 9). The behavior of **1** in these organocatalyzed reactions is remarkable, bearing in mind that enantioselective generation of tetrasubstituted carbon stereocenters remains a considerable challenge.



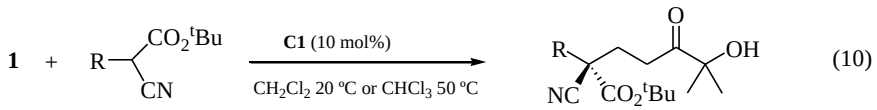
Selected catalysts (Ar: 3,5-$(F_3C)_2C_6H_3$):

(9)

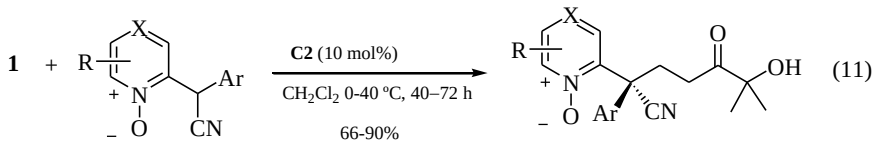


(i) Addition of α-substituted cyanoacetates

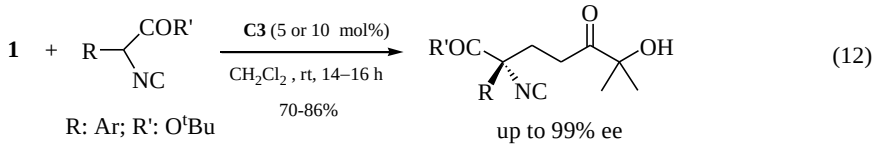
α-Substituted cyanoacetates have been shown to be poorly reactive substrates in conjugate addition reactions, particularly against alkyl vinyl ketones. However, hydroxy enone **1** reacts with both α-aryl and α-alkyl *tert*-butyl cyanoacetates in the presence of the squaramide catalyst **C1**.[2] In general, the reactions with α-aryl cyanoacetates proceed well at room temperature to afford, after 1 h, adducts in excellent yields and enantioselectivities, while α-alkylcyanoacetates usually require longer times (24–30 h) and higher temperatures (about 50 ºC) (eq 10). β-Substituted analogs of **1** have also been used for this reaction with excellent results.[2]



(10)



(11)



(12)

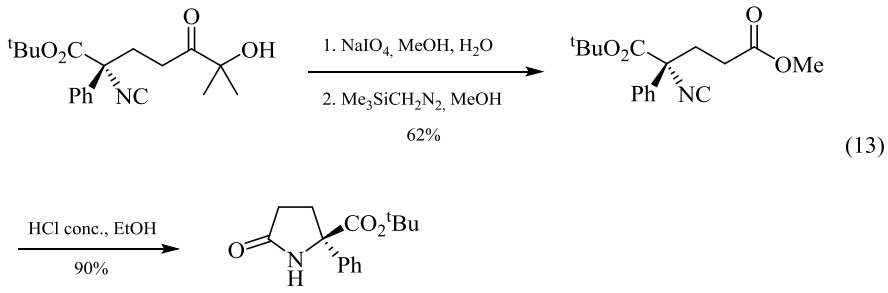
(ii) Addition of α-substituted 2-(cyanomethyl)azaarene N-oxides

2-Cyanomethylpyridine (and pyrazine) N-oxides react with **1** in the presence of some bulky squaramide/tertiary amine catalysts (e.g. **C2**) to afford the elusive 2-*tert*-alkyl azaaryl adducts with enantioselectivities up to 94% *ee*[13] (eq 11). Key for success is the N-oxide functionality of substrates that acts as a removable activating and stereodirecting group. The reactions proceed well with α-aryl 2-(cyanomethyl)azaarene N-oxides in about 40–72 h, but work sluggish with the corresponding α-alkyl series.

(iii) Additions of α-substituted isocyano(thio)acetates

The enantioselective conjugate addition of both α-aryl isocyanoacetates and α-alkyl isocyanothioacetates to hydroxy enone **1** has been performed using squaramide/tertiary amine catalysts featuring a sterically congested polyaryl side-arm (e.g. **C3**)[14] (eq 12). With the former, the reactions proceed in good yields and excellent enantioselectivity (up to 99% *ee*) at room temperature using 5 mol% catalyst to give the corresponding adducts in about 14 h, with *o*-substituted aryl isocyanoacetates being an exception. Under these

conditions, α-alkyl isocyanoacetates were not competent reaction partners. However, α-benzyl isocyanothioacetates with a di-*ortho* substituted phenyl thioester group react satisfactorily affording products in 96% *ee* and without formation of undesired byproducts. Transformation of adducts into pyroglutamate esters is achieved through oxidative cleavage of the acyloin moiety, subsequent methylation and final treatment with ethanolic HCl (eq 13).



(13)

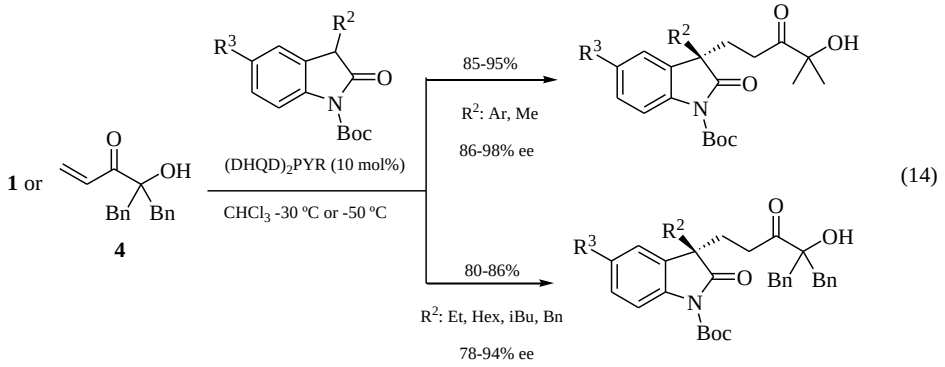
Variations of reagent 1 for reaction fine tune

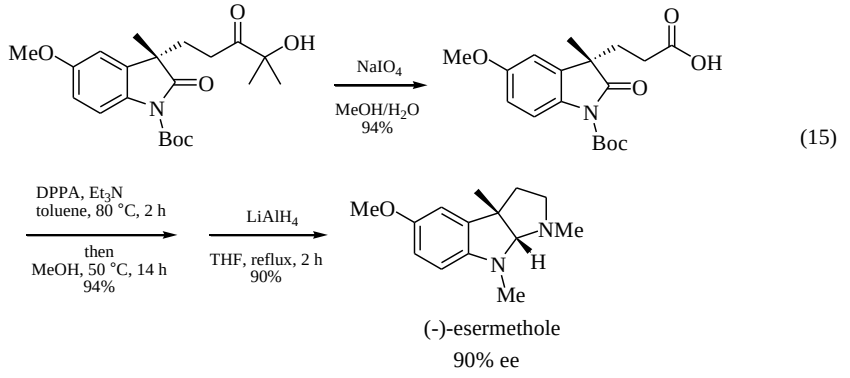
Variants of reagent **1** with slightly modified ketol moiety are easy to prepare, leading to analogs with eventually improve reactivity/selectivity profiles. Both the geminal R substituents at α-carbon[12e] and the OH group of ketol are potential sites for structural modification providing a short library of acrylate equivalents for screening and best fitting to the specific steric and/or electronic requirements of a given catalytic settings.

a) Variation at the geminal R groups (additions of 3-substituted oxindoles)

Hydroxy enone **1** reacts with 3-aryl oxindoles (R^2= Ar) in the presence of commercially available $(DHQD)_2PYR$ catalyst to give the corresponding Michael adducts in excellent yields and enantioselectivities[2] (eq 14). However, while 3-methyl oxindoles (R^2= Me) works also well, reactions involving superior 3-alkyl oxindoles (R^2= Et, Hex, iBu, Bn)

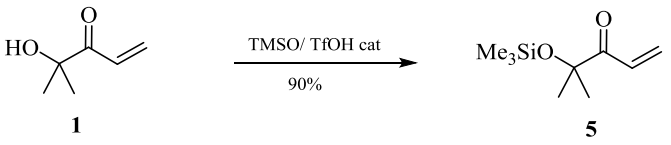
are accompanied with poor enantiocontrol (30–56% *ee*). This limitation could be surmounted by using the analog **4**, featuring two benzyl groups at Cα, which provides the corresponding addition adducts with high selectivity. Elaboration of the ketol moiety in one adduct has served to synthesize (–)-esermethole in few steps (eq 15).





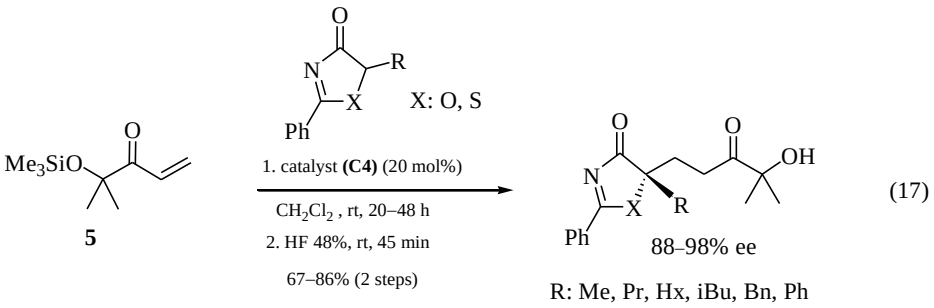
b) O-Silyl analogs (additions of heterocyclic C-nucleophiles)

While the role played by the free OH group of **1** is crucial in most of the cases for achieving high reactivity and stereoselectivity, in some particular substrate combinations the O-$SiMe_3$ derivative, easily prepared by silylation of **1** with 3-(trimethylsilyl)-2-oxazolidinone (TMSO) and catalytic trifluoromethanesulfonic acid (eq 16),[2] proved to be superior.



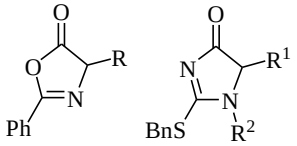
1 **5** (16)

Several heterocycles susceptible for a soft enolization successfully react with trimethylsilyloxy enone **5** in the presence of a squaramide/Brønsted base catalyst. For instance, 5*H*-oxazol-4-ones and 5*H*-thiazol-4-ones react with **5** in the presence of 20 mol% catalyst **C4** with generation of a new tetrasubstituted carbon center in enantioselectivities from good to excellent (eq 17).[2] Adducts with free ketol moiety were isolated by one pot treatment of crude products with HF or AcOH. Other heterocyclic nucleophiles suitable for reaction with **5** includes 4*H*-oxazol-5-ones,[2] and 1*H*-imidazol-4(5*H*)-ones.[15]

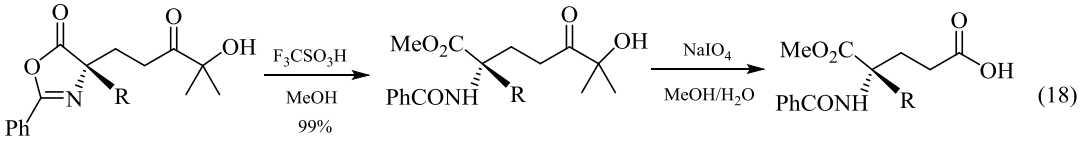


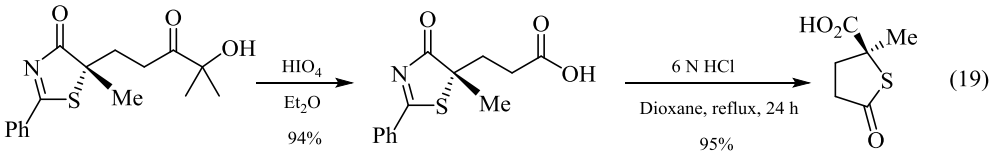
(17)

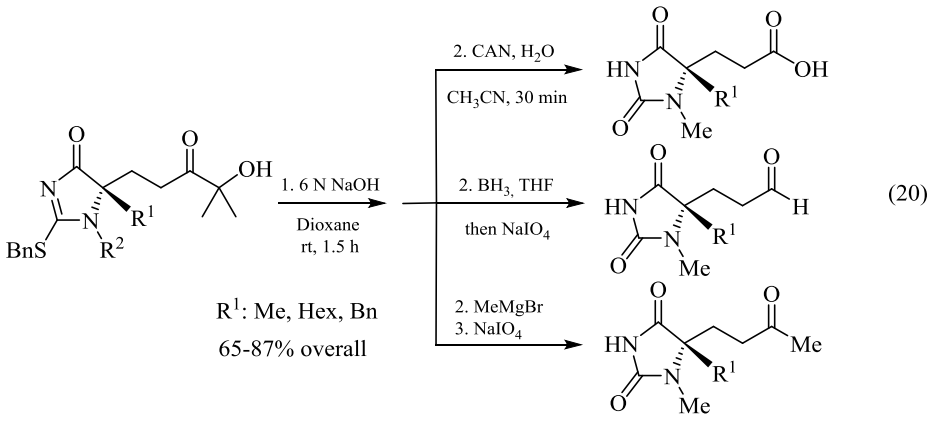
Other suitable nucleophiles:



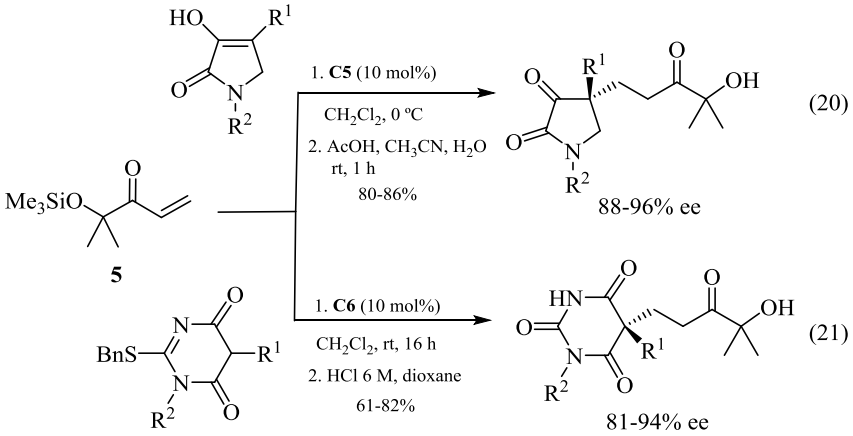
These reactions are of significant synthetic relevance since the resulting adducts give access, through simple hydrolytic conditions and ketol elaboration, to α-hydroxy, α-thio, and α-amino acid derivatives, including hydantoins, as shown in eq 18–20.



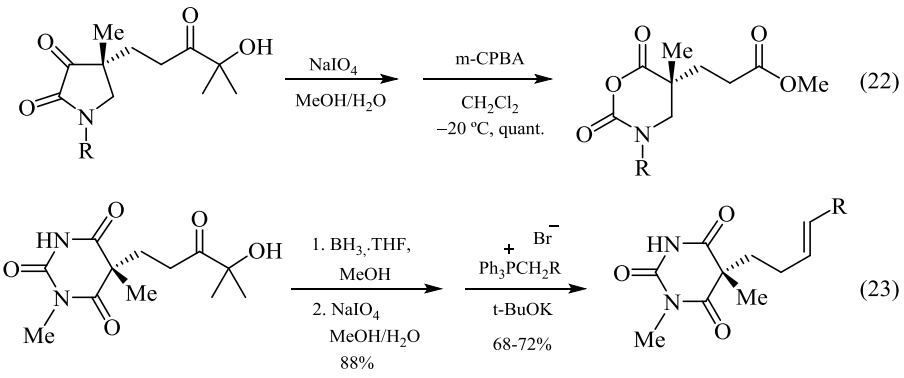




The potential of reagent **5** as an equivalent of acrylate/acrolein in asymmetric catalysis is further illustrated in its enantioselective Michael-type reactions with 4-substituted pyrrolidine-2,3-diones[16] and 2-benzylthio-4,6-dioxopyrimidines[17] leading to all-carbon quaternary stereocenters. Upon desilylation, adducts are obtained in good yields and excellent enantiomeric excess (eq 20–21).

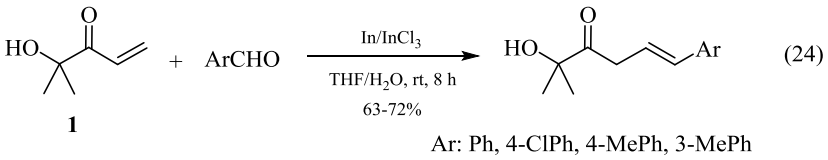


Oxidative elaboration of the ketol moiety followed with a Baeyer-Villiger oxidation (eq 22) or a Wittig olefination (eq 23) affords in good yields useful building blocks, such as N-carboxy anhydrides of β-amino acids or barbituric acids, respectively, featuring a quaternary carbon stereosenter.



Miscellaneous

Coupling of **1** with aromatic aldehydes mediated by In/$InCl_3$ system[18] in a THF/water mixture proceed at room temperature producing β,γ-unsaturated hydroxy ketones in good yield (eq 24). These homologated ketols have been used as donor ester equivalents in the context of Brønsted base catalyzed direct Michael reaction with nitroolefins.[19]



β-Substituted analogs of **1** also participate as enal surrogates in several annulation processes promoted by N-heterocyclic carbene (NHC) catalysts which proceed through a Breslow dienol intermediate with evolution of acetone. Upon reaction with the corresponding dienophile, this process affords cyclopentenes (with enones),[20] bicyclic sulfonyl imides (with cyclic sulfonylimines)[20] or dihydropyridinones (with vinylogous amides).[21] NHC mediated reactions of β-substituted analogs of **1** with amines lead to

amides.[22] Such an acylation reaction has been implemented into a kinetic resolution of cyclic secondary amines.[23]

1. Hoff, S.; Brandsma, L.; Arens, J. F., *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179.
2. Badiola, E.; Fiser, B.; Gómez-Bengoa, E.; Mielgo, A.; Olaizola, I.; Urruzuno, I.; García, J. M.; Odriozola, J. M.; Razkin, J.; Oiarbide, M.; Palomo, C., *J. Am. Chem. Soc.* **2014**, *136*, 17869.
3. Palomo, C.; Oiarbide, M.; García, J. M., *Chem. Soc. Rev.* **2012**, *41*, 4150.
4. Masamune, S.; Red III, L. A.; Davis, J. T.; Choy, W., *J. Org. Chem.* **1983**, *48*, 4441.
5. Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A., *J. Am. Chem. Soc.* **2003**, *125*, 13942.
6. Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Lecumberri, A.; Linden, A., *J. Am. Chem. Soc.* **2002**, *124*, 10288.
7. Bañuelos, P.; García, J. M.; Gómez-Bengoa, E.; Herrero, A.; Odriozola, J. M.; Oiarbide, M.; Palomo, C.; Razkin, J., *J. Org. Chem.* **2010**, *75*, 1458.
8. Pfeiffer, M. W. B.; Phillips, A. J., *J. Am. Chem. Soc.* **2005**, *127*, 5334.
9. Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; González, A.; Linden, A., *Angew. Chem. Int. Ed.* **2005**, *44*, 6187.
10. (a) Palomo, C.; Oiarbide, M.; García, J. M.; Bañuelos, P.; Odriozola, J. M.; Razkin, J.; Linden, A., *Org. Lett.* **2008**, *10*, 2637. (b) García, J. M.; Maestro, M. A.; Oiarbide, M.; Odriozola, J. M.; Razkin, J.; Palomo, C., *Org. Lett.* **2009**, *11*, 3826.
11. Iriarte, I; Vera, S.; Badiola, E.; Mielgo, A.; Oiarbide, M.; García, J. M.; Odriozola, J. M.; Palomo, C., *Chem. Eur. J.* **2016**, *22*, 13690.
12. (a) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (b) Yang, L.; Zhu, Q.; Guo, S.; Qian, B.; Xia, C.; Huang, H., *Chem. Eur. J.*, **2010**, *16*, 1638. (c) García, J. M.; González, A.; Kardak, B. G.; Odriozola, J. M.; Oiarbide, M.; Razkin, J.; Palomo, C., *Chem. Eur. J.* **2008**, *14*, 8768. (d) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M., *J. Am. Chem. Soc.* **2004**, *126*, 9188. (e) Palomo, C.; Pazos, R.; Oiarbide M.; García, J. M., *Adv. Synth. Catal.*, **2006**, *348*, 1161. (f) Monge, D. ; Martín-Zamora, E. ; Vázquez, J. ; Alcarazo, M. ; Alvarez, E. ; Fernández R. ; Lassaletta, J. M., *Org. Lett.*, **2007**, *9*, 2867. (g) Lee, S.; Lim, C.J. ; Kim, S. ; Subramaniam, R. ; Zimmerman, J. ; Sibi, M. P., *Org. Lett.*, **2006**, *8*, 4311.
13. Izquierdo, J.; Landa, A.; Bastida, I.; López, R.; Oiarbide, M.; Palomo, C., *J. Am. Chem. Soc.* **2016**, *138*, 3282.
14. Odriozola, A.; Oiarbide, M.; Palomo, C., *Chem. Eur. J.* **2017**, *23*, 12758.
15. Etxabe, J.; Izquierdo, I.; Landa, A.; Oiarbide, M.; Palomo, C., *Angew. Chem. Int. Ed*. **2015**, *54*, 6883.
16. Badiola, E.; Olaizola, I.; Vázquez, A.; Vera, S.; Mielgo, A.; Palomo, C., *Chem. Eur. J.* **2017**, *23*, 8185.
17. del Pozo, S.; Vera, S.; Oiarbide, M.; Palomo, C., *J. Am. Chem. Soc.* **2017**, *139*, 15308.
18. Kang. S.; Jang, T-S.; Keum, G.; Kang, S. B.; Han, S-Y.; Kim, Y., *Org. Lett.* **2000**, *2*, 3615.
19. Iriarte, I.; Olaizola, O.; Vera, S.; Gamboa, I.; Oiarbide, M.; Palomo, C., *Angew. Chem. Int. Ed*. **2017**, *56*, 8860.
20. Chiang, P-C.; Rommel M.; Bode, J. W., *J. Am. Chem. Soc.* **2009**, *131*, 8714.
21. Wanner, B.; Mahatthananchai, J.; Bode, J. W., *Org. Lett.* **2011**, *13*, 5378.

22. Chiang, P-C.; Kim, Y.; Bode, J. W., *Chem. Commun*. **2009**, 4566.
23. Binanzer, M.; Hsieh, S-Y.; Bode, J. W., *J. Am. Chem. Soc.* **2011**, *133*, 19698.