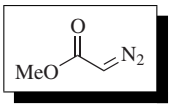
Methyl Diazoacetate[1]



[6832-16-2] $C_3H_4N_2O_2$ (MW 100.09)

InChI = 1/C3H4N2O2/c1-7-3(6)2-5-4/h2H,1H3
InChIKey = MIVRMHJOEYRXQB-UHFFFAOYAG

(cyclopropanation of alkenes,[2–11] heteroarenes,[12–15] and imines;[16,17] cyclopropenation of alkynes;[4,19] addition to aromatic substrates;[20,21] insertion into polar X–H,[22–24] C–X,[25,26] and C–C bonds;[27] condensation with carbonyls;[28] 1,3 dipolar cycloaddition with enamines[29] and alkynes,[30] yielding substituted pyrazolines and pyrazoles; [3 + 2] cycloadditions via ylides[31])

Physical Data: bp 39–43 °C/10 mmHg.

Solubility: sol diethyl ether, dichloromethane, chloroform, benzene.

Preparative Method: from methyl glycinate hydrochloride and sodium nitrite upon treatment with a 5% solution of sulfuric acid.[37]

Handling, Storage, and Precautions: extreme caution should be exercised in handling methyl diazoacetate since it is thermally unstable and has been found to detonate if heated rapidly or overheated (do not expose to temperatures >50 °C), emitting toxic fumes of NO_x. Diazo esters are also toxic and should be handled in a well-ventilated fume hood.

Original Commentary

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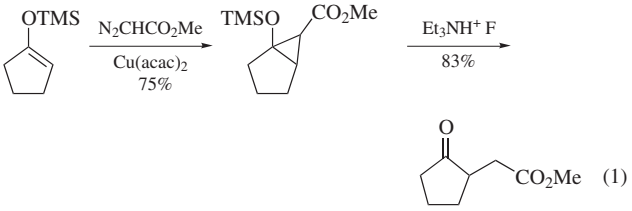
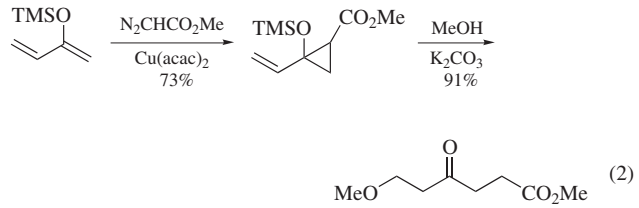
Cyclopropanation. Under catalytic conditions, methyl diazoacetate readily forms an ester carbenoid which adds to a variety of alkenes, yielding cyclopropyl esters. ***Dirhodium(II) Tetraacetate*** effectively catalyzes the addition of methyl diazoacetate to *cis*-2-octene.[2] Substituted conjugated dienes can be selectively cyclopropanated with methyl diazoacetate.[30] The observed regio- and stereoselectivity is determined by the choice of catalyst and the electronic characteristics of the diene. The enantioselective cyclopropanation of an alkene with methyl diazoacetate can be achieved with the use of a chiral catalyst.[31] Methyl diazoacetate reacts under copper catalysis with the trimethylsilyl enol ether of cyclopentanone to give a silyloxycyclopropane. Treatment with a fluoride source yields a 1,4-keto ester (eq 1).[32,33]



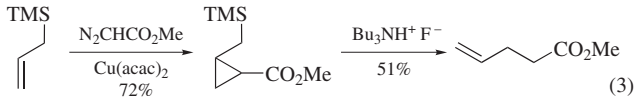
(1)

2-(Trimethylsilyloxy)buta-1,3-diene can be cyclopropanated in a regioselective manner with methyl diazoacetate and ***Copper(II) Acetylacetonate***. Subsequent nucleophilic addition of methanol yields methyl 6-methoxy-4-oxohexanoate in excellent yield (eq 2).[38]



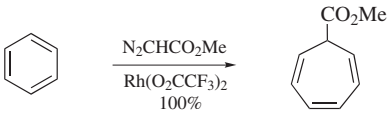
(2)

A number of 6- or 7-functionalized 4-oxoalkanoates can be prepared utilizing this protocol with a variety of Michael adducts. Methyl diazoacetate addition to ***Allyltrimethylsilane*** followed by treatment with ***Tetrabutylammonium Fluoride*** yields methyl 4-pentenoate (eq 3).[39] Cyclopropyl boronates[4] and cyclopropyl amines[40] can also be prepared from methyl diazoacetate under catalytic conditions.



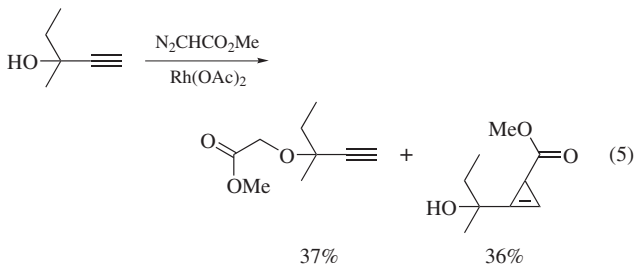
(3)

The addition of the methyl diazoacetate-derived carbene to benzene gives rise to methyl cyclohepta-2,4,6-triene-1-carboxylate with a high degree of selectivity (eq 4).[27] The rhodium-catalyzed addition to substituted phenyls yields an isomeric mixture of products. In addition to substituted phenyls, methyl diazoacetate can add to various aromatic hetrocycles.[28]



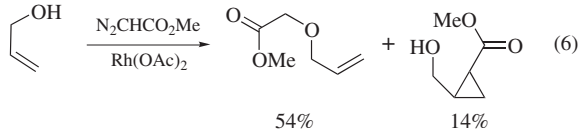
(4)

Cyclopropenation. Cyclopropenyl esters are formed by the addition of methyl diazoacetate to various alkynes using $Rh(OAc)_2$ as the catalyst.[5] This cyclopropenation protocol is incompatible with alkynic alcohols (eq 5).[18] The catalyzed insertion of methyl diazoacetate into the O–H bond successfully competes with cyclopropene formation. High enantioselectivity can be achieved in a cyclopropenation with the use of a chiral dirhodium(II) carboxylate.[6]



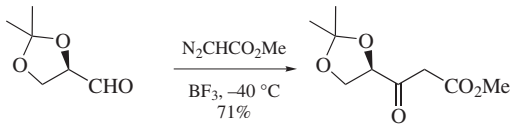
(5)

Insertion. The insertion of methyl diazoacetate into the X–H bond (where X = S or O) is catalyzed efficiently with rhodium carboxylates.[22,43] The catalyzed insertion into allyl alcohol yields an α-alkoxy ester (eq 6).[44] Mild selectivity can be achieved over a competitive cyclopropanation with an appropriate catalyst.



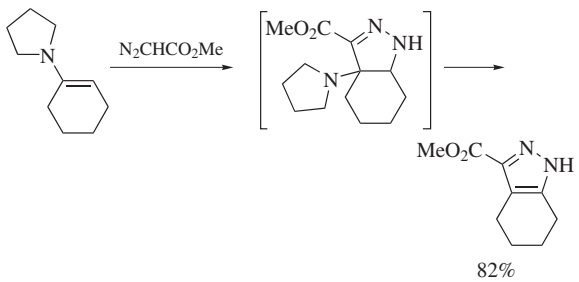
(6)

Condensation. Lewis acid-catalyzed addition of methyl diazoacetate to an aldehyde provides a convenient method for the preparation of a 1,3-dicarbonyl. Treatment of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl diazoacetate yielded methyl (4*R*)-4,5-*O*-isopropylidene-3-keto-4,5-dihydroxypentanoate in good yield (eq 7).[45]



(7)

1,3-Dipolar Cycloaddition. The uncatalyzed 1,3-dipolar cycloaddition of methyl diazoacetate with a suitable dipolarophile yields a substituted pyrazoline or pyrazole.[29,30,46] *N*-(1-Cyclohexenyl)pyrrolidine reacts with methyl diazoacetate, yielding a pyrazoline which eliminates pyrrolidine to give a pyrazole in excellent yield (eq 8).



(8)

First Update

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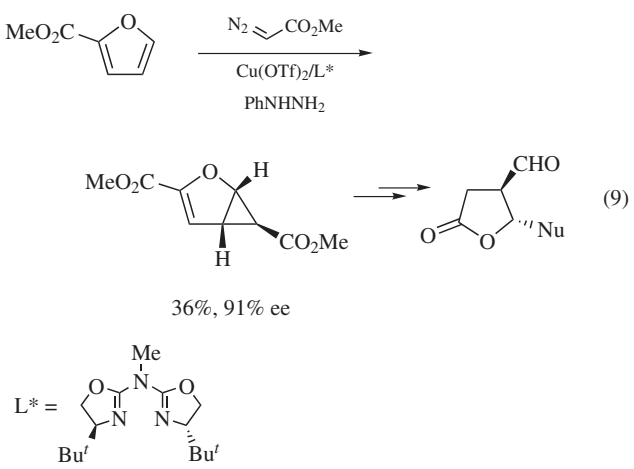
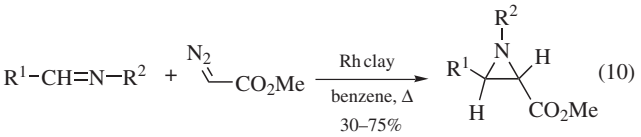
Cyclopropanation. The most important application of methyl diazoacetate continues to be the transition metal-catalyzed carbene additions to alkenes, although the corresponding ethyl diazoacetate generally gives better results in these reactions. With the development of semicorrine,[4] bis(oxazoline)[5] and azabis(oxazoline)[6] ligands, chiral copper(I) catalysts are now available that allow the synthesis of methyl cyclopropylcarboxylates with high optical induction. Next to acyclic alkenes, glycals[7] and heteroarenes such as pyrrols[12] and furans[13] (eq 9) seem to be especially useful substrates, giving facile access to unnatural amino acids[14] and disubstituted γ-butyrolactones.[15]



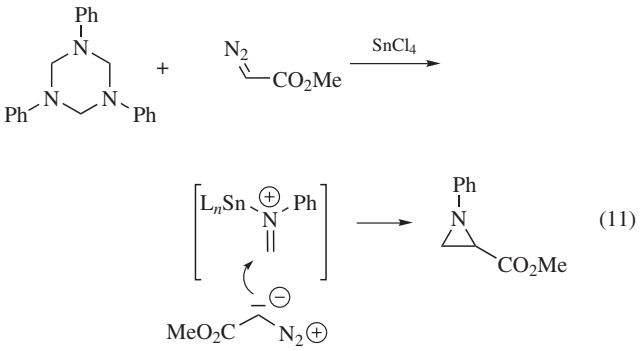
(9)

Besides chiral copper catalysts, ruthenium complexes with salene,[8] pyridinebis(oxazoline),[9] or porphyrin[10] ligands have been employed in asymmetric cyclopropanation reactions of alkenes. Also rhodium catalysts have been met with some success in the carbene transfer onto alkenes,[11] but importantly also onto imines to allow the synthesis of aziridines (eq 10).[16]



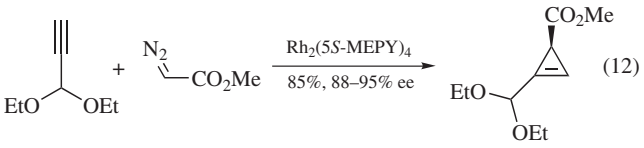
(10)

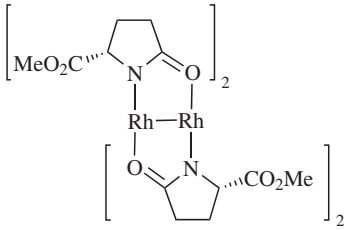
Hexahydro-1,3,5-triazines can be used as precursor, from which imines can be liberated in situ upon treatment with Lewis acids such as $SnCl_4$, which activate at the same time the imine for nucleophilic addition of methyl diazoacetate (eq 11).[17]



(11)

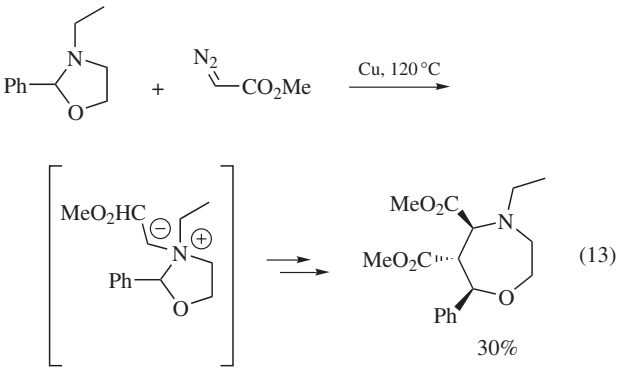
Cyclopropenation. Chiral dirhodium(II) tetracarboxylates are the catalysts of choice for carbene transfer to alkynes. The carbene adduct of 1,1-diethoxypropyne (eq 12) has proved to be a versatile starting material for a broad variety of *cis*-disubstituted cyclopropanes with high optical purity.[19]



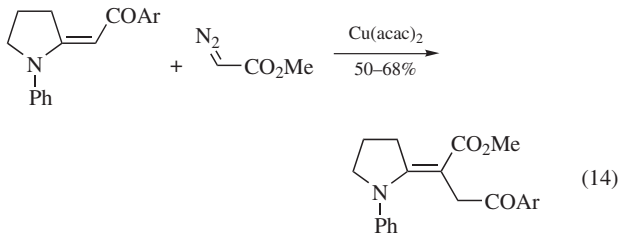


$Rh_2(5S\text{-MEPY})_4$

Insertion. While intermolecular insertion into C–H bonds is not particularly effective with methyl diazoacetate,[23] contrasting donor-acceptor-substituted diazo compounds, insertion into X–H bonds (X = O, S) readily occurs when catalyzed by rhodium(II).[24] Making use of ylide intermediates (eq 13), copper catalysts are able to promote formal insertions into C–O[25] and C–N[26] bonds, although selectivities and yields obtained to date are not particularly high.

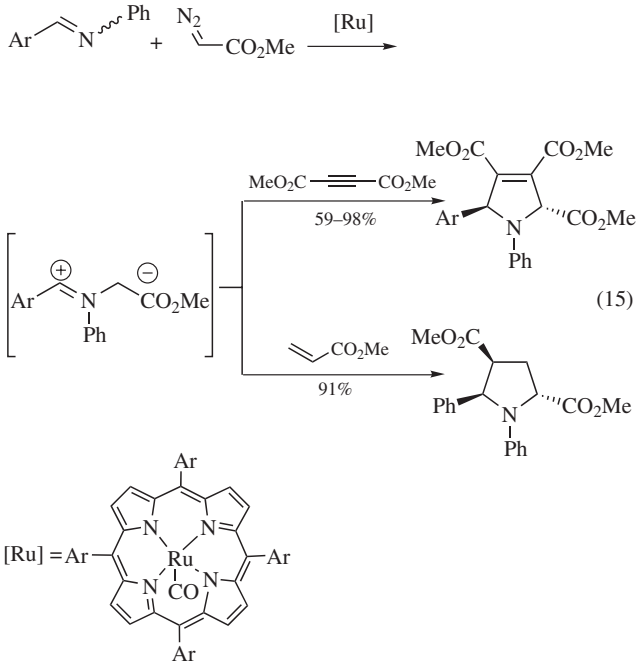


Utilizing the tendency of donor-acceptor-substituted cyclopropanes to readily undergo ring-opening, carbene transfer to enamino ketones leads to enamino esters, which constitute formal products of C–C insertion of the carbene unit (eq 14).[27] Interestingly, it was found that copper(II) acetylacetonate is more effective to achieve this transformation than copper(I) triflate or dirhodium tetraacetate, being more commonly employed as catalysts for reactions with diazoacetates.



Ar = 2-thienyl, 2-furyl, 4-OMe-Ph, 4-Cl-Ph

[3 + 2] Cycloaddition Via Ylides. Three-component coupling reactions of methyl diazoacetate with *N*-benzylidene imines and alkenes or alkynes are catalyzed by ruthenium porphyrins (eq 15).[31] Initial carbene transfer to the imines generates azomethine ylides that undergo dipolar [3 + 2] cycloadditions to form pyrrolidines with high diastereoselectivity.



Related Reagents. Diazoacetaldehyde; Diazoacetone; Dimethyl Diazomalonate; Ethyl Diazoacetate.

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