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Catalytic Addition Methods for the Synthesis of Functionalized Diazoacetoacetates and Application to the Construction of Highly Substituted Cyclobutanones

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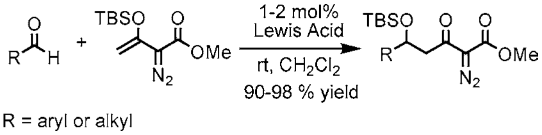
ABSTRACT



Methyl 3-(trialkylsilanyloxy)-2-diazo-3-butenoate undergoes Lewis acid-catalyzed Mukaiyama aldol addition with aromatic and aliphatic aldehydes in the presence of low catalytic amounts of Lewis acids in nearly quantitative yields. Scandium(III) triflate is the preferred catalyst and, notably, addition proceeds without decomposition of the diazo moiety. Diazoacetoacetate products from reactions with aromatic aldehydes undergo rhodium(II)-catalyzed ring closure to cyclobutanones with high diastereocontrol. Examples of complimentary Mannich-type addition reactions with imines are reported.

Diazoacetoacetates are widely used in catalytic metal carbene reactions.[1,2] Generally prepared by alcohol condensation with diketene or its surrogate,[3,4] followed by diazo transfer,[5] diazoacetoacetates exhibit higher thermal and acid stability than do their diazoacetate counterparts, and they often offer greater reaction control in transformations following diazo decomposition.[1,6] Catalytic reactions of diazoacetoacetates involving addition, insertion, and association (ylide-derived processes) that produce cyclopropanes, cycloalkanone structures, and β-lactams are well documented.[1,2,7] Chemical modifications with diazocarbonyl compounds have been of long-standing interest,[1] and both acid and base promoted aldol reactions have been developed for this purpose. However, these reactions generally result in the loss of the diazo functionality.[8] Although earlier studies have shown that

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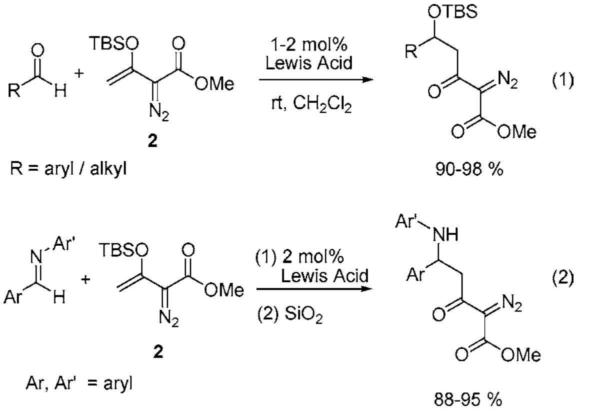
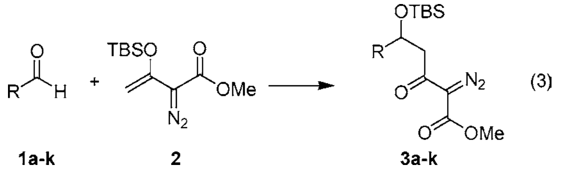
condensation of ethyl diazoacetate with aldehydes and ketones can occur with retention of the diazo group,[9−11] only recently have methods involving Lewis acids been used to couple diazoacetates with aldehydes. Boron[12] and titanium(IV)[13] enolates of diazoacetoacetates have been reported to undergo condensation with aldehydes, but stoichiometric amounts of the Lewis acids were required to achieve full conversion, and these reactions occurred at −78 °C. We now report that the use of lanthanide triflates, especially scandium(III) triflate, in low catalytic amounts is highly effective for Mukaiyama aldol addition reactions of methyl 3-(*tert*-butyldimethylsilanoxy)-2-diazobut-3-enoate (**2**)[14] with both aliphatic and aromatic aldehydes at room temperature (eq 1, Scheme 1), and that the same catalysts promote Mannich addition of **2** with imines (eq 2, Scheme 1). In both sets of transformations the diazo functionality is retained, and product yields are nearly quantitative.

Scheme 1



Catalytic Mukaiyama aldol addition reactions of aldehydes with silyl enol ethers have been achieved by using a broad selection of catalysts.[15] Using the same methodology as with TMS-vinyl ethers,[15,16] but with the acid-sensitive diazo functionality of silyl enol ethers of methyl diazoacetoacetate, we evaluated the potential of this methodology with a selection of Lewis acids. In addition to achieving high product yields, our criteria included the use of catalyst loadings below 5 mol % and to have reactions occur at or near room temperature. Our survey using the TBDMS derivative **2** and benzaldehyde identified the lanthanide(III) triflates as the most promising, and efforts were undertaken to determine the breadth of application. As indicated in Table 1, nearly quantitative yields of aldol addition reaction products (eq 3) were obtained with both aliphatic and aromatic aldehydes, and scandium(III) triflate was the catalyst of choice. In all cases the diazo functionality was found to remain intact throughout the reaction and during workup.

Table 1. Lewis Acid-Catalyzed Mukaiyama Aldol Addition Reactions of **2** with Representative Aldehydes[a]



aldehyde	R	yield (%) of $\mathbf{3}^{b}$		
		Sc(OTf)$_3$	La(OTf)$_3$	Cu(OTf)$_2$
1a	4-MeOC$_6$H$_4$	98	90	82
1b	4-MeC$_6$H$_4$	97	89	77
1c	Ph[c]	93	90	76
1d	4-ClC$_6$H$_4$	98	91	76
1e	4-CF$_3$ C$_6$H$_4$	94		
1f	4-NO$_2$C$_6$H$_4$[d]	0	0	0
1g	*trans*-β-styryl	89	88	
1h	BnOCH$_2$	93	93	72
1i	COOEt	91		
1j	*n*-heptyl	94	93	
1k	*n*-propyl[e]	92		

[a] Aldehyde (1.5 mmol) was added to a solution of vinyldiazoacetate **2** (2.2 mmol) and metal triflate (2.0 mol %) in CH$_2$Cl$_2$ (3 mL) and stirred at room temperature for 10 h. [b] Yield of isolated **3** following column chromatography. [c] Use of 1.0 mol % catalyst gave 90% yield of **3c** and use of 0.1 mol % catalyst gave **3c** in only 5% yield after 10 h. [d] Unreacted aldehyde and **2** were the only materials recovered after 10 h. [e] Isolated yield for the deprotected Mukaiyama aldol adduct (see the Suppoting Information).

Scandium(III), lanthanum(III), ytterbium(III), and copper(II) triflates were all effective under conditions of low catalyst loading (1−2 mol %) for addition reactions performed between **2** and representative aldehydes (Table 1).[17] Reactions were generally complete within 10 h at room temper-

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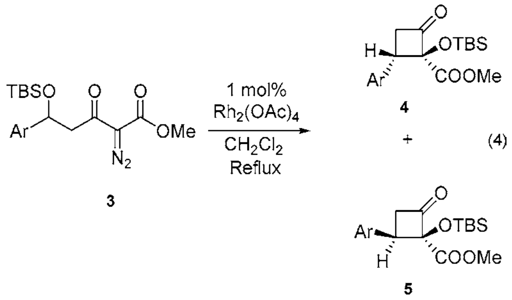
(17) Typical Mukaiyama aldol addition procedure: To a dry 5-mL round-bottomed flask fitted with a septum was added anhydrous scandium(III) triflate (14 mg, 0.030 mmol) and 3.0 mL of anhydrous dichloromethane. Vinyldiazoacetate **2** (564 mg, 2.20 mmol) was then added dropwise over 5 min, using a 1 mL syringe, followed by aldehyde (1.50 mmol). The reaction mixture was stirred at room temperature for 10 h, during which time the color of the solution changed from orrange to pale yellow. (The reactions with **1a** and **1c** were found to be incomplete after 6 h.) The product was isolated by flash column chromatography on silica gel, eluting with 9:1 hexane/ethyl acetate.

ature, but those catalyzed by $Yb(OTf)_3$ were sluggish under these same conditions.[18] The only exception to the generality of this process among the aldehydes that were employed is *p*-nitrobenzaldehyde, which did not participate in reactions with **2** and any member of this catalyst selection. That this is exceptional is indicated by results with 4-α,α,α-trifluorotolualdehyde, which produced the addition product **3e** with very high conversions despite the presence of the strongly electron-withdrawing trifluoromethyl group. With copper(II) triflate, the yields of condensation products **3** were comparably low due to, we believe, slow decomposition of the diazo moiety of **2** and/or **3**. Reactions performed with the TMS analogue of **2** underwent condensation at a faster rate than **2** to give comparable yields of TMS-**3**. However, the TBDMS protective group provided greater stability in **2** and to the condensation products, and they were easier to handle than those with TMS protection.

The potential of this addition process for synthetic transformations achieved through diazo decomposition was explored by reactions performed with rhodium acetate. Diazo decomposition of the Mukaiyama aldol adducts **3b**−**d** in the presence of 1.0 mol % rhodium(II) acetate led to the formation of highly substituted cyclobutanones (eq 4) in high yields and with high diastereoselectivity (Table 2).

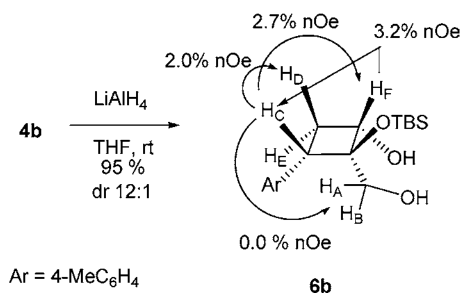
Table 2. Cyclobutanone Formation by Rhodium Acetate-Catalyzed Diazo Decomposition of **3**[a]



adduct	Ar	yield, %[b] 4 + 5	4:5[c]
3b	4-Me-C_6H_4	84	12:1
3c	Ph	80	10:1
3d	4-Cl-C_6H_4	84	10:1

[a] The Mukaiyama aldol adduct (1.0 mmol) in CH_2Cl_2 (2 mL) was added via a syringe pump over 5 h to a refluxing solution of $Rh_2(OAc)_4$ (1.0 mol %) in 2 mL of CH_2Cl_2. [b] Isolated yield of **4** + **5**. [c] Determined by integration of the characteristic ^1H NMR signals of **4** (δ 3.37 ppm) and **5** (δ 3.39 ppm).

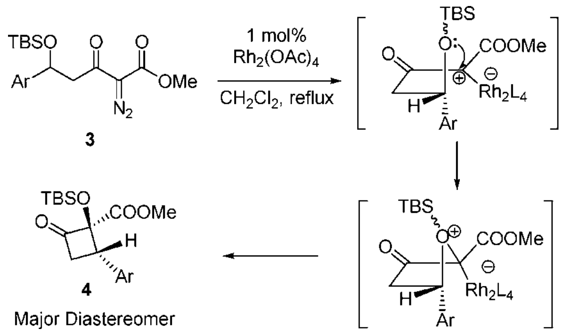
Scheme 2



Experiments to determine the relative stereochemistry of substituents in **4b** directly were inconclussive. However, reduction of **4b** by lithium aluminum hydride[19] produced a diol (**6b**) from which nOe experiments provided evidence for the relative stereochemistry reported in Table 2 (Scheme 2). These experiments place the carbomethoxy and the aryl groups on the same face of the cyclobutanone ring of the major isomer **4**.

These surprisingly clean reactions did not form products from either formal aromatic substitution or aromatic cycloaddition,[1] nor was carbon−hydrogen insertion into the benzylic position observed. Instead, this method provides a straightforward synthesis of highly substituted cyclobutanones via the oxonium ylide pathway described in Scheme 3. The synthesis of highly substituted cyclobutanes with multiple stereogenic centers is considered to be a challenging task,[20] and to our knowledge there has only been one prior report of cyclobutanone formation through oxonium ylides.[21]

Scheme 3



Extension of the aldol addition reaction methodology to reactions of **2** with benzylideneanilines (eq 5) produced the results that are reported in Table 3.

Reactions were performed at room temperature with an equivalent amount of imine and **2**. Results with scandium(III) triflate at 2.0 mol % were optimum and are reported. As expected with the results from Mukaiyama aldol addition reactions with **2** (Table 1), the diazo functionality was retained in these Mannich reactions. The TBDMS protective group comes off nitrogen upon passing the reaction mixture through a short plug of silica gel to remove catalyst. Curiously, the basic nature of reactant and product in this transformation does not change the catalytic loading relative to that used for reactions with aldehydes. This previously

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(18) Under similar conditions, use of 2 mol % of $Yb(OTf)_3$ produced 77% **3a**, 77% **3b**, 75% **3c**, and 72% **3d**.

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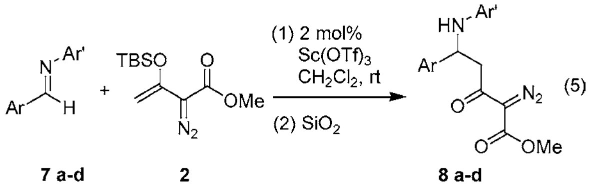
Table 3. Lewis Acid-Catalyzed Mannich Addition of Benzylideneanilines to **2**[a]



imine	Ar	Ar′	yield (%) of **8**[b]
7a	4-MeOC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	95
7b	4-ClC$_6$H$_4$	Ph	90
7c	Ph	4-NO$_2$C$_6$H$_4$	93
7d	Ph	Ph	88

[a] Imine (1.5 mmol) in CH$_2$Cl$_2$ (1 mL) was added to a solution of vinyldiazoacetate **2** (2.2 mmol) and scandium(III) triflate (2.0 mol %) in CH$_2$Cl$_2$ (2 mL) then stirred at room temperature for 10 h. [b] Yield of isolated **8** following column chromatography.

unreported Mannich-type addition methodology to form substituted diazoacetoacetates directly may be a viable alternative to the approach of effecting diazo transfer to the amine-substituted acetoacetate.[7a,b] Davis has reported that analogues of **8** undergo highly selective intramolecular N—H insertion catalyzed by Rh$_2$(OAc)$_4$.[7a]

In summary, we have developed efficient Mukaiyama aldol and Mannich addition reactions of readily accessible diazo-containing silyl enol ether with aldehydes and imines using low catalytic amounts of commercially available Lewis acids. The synthetic utility of the Mukaiyama aldol adduct has been demonstrated with the highly diastereoselective, facile rhodium(II) acetate-catalyzed syntheses of highly substituted cyclobutanones. Work is continuing to develop the full synthetic potential of this methodology.

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

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