DOI: 10.1002/ejoc.200900475

Morita–Baylis–Hillman Reactions Between Conjugated Nitroalkenes or Nitrodienes and Carbonyl Compounds

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Dedicated to Professor D. Basavaiah[‡]

Keywords: Alkenes / α-Hydroxyalkylation / C–C coupling / Nitroalkenes / Morita–Baylis–Hillman (MBH) reaction / Synthetic methods

Morita–Baylis–Hillman (MBH) reactions between conjugated nitroalkenes or nitrodienes and various carbonyl compounds such as glyoxylate, trifluoropyruvate, pyruvaldehyde, oxomalonate, ninhydrin, and formaldehyde have been extensively investigated. The reactions proceeded smoothly in the presence of DMAP (40–100 mol-%) in acetonitrile and in some cases also in that of imidazole (100 mol-%) in $CHCl_3$ or THF, to provide the multifunctional adducts in good to excellent yields. The reactions catalyzed by DMAP in acetonitrile were superior to the imidazole-catalyzed reactions both in terms of the rate of reaction and in terms of the isolated yields of the MBH adducts. The catalytic roles played by DMAP and imidazole in these reactions, vis-à-vis other MBH catalysts such as DABCO, are attributed primarily to resonance stabilization of the initial zwitterionic intermediates. Whereas the *E* isomers are the major or exclusive products in the cases of glyoxylate, pyruvaldehyde, and formaldehyde, the *Z* isomers predominate in the cases of trifluoropyruvate and ninhydrin. Interestingly, oxomalonate forms *E* isomers with aromatic nitroalkenes and *Z* isomers with aliphatic ones. These selectivities and the formation of unusual deconjugated products in the case of certain β-alkyl-nitroethylenes have been explained.

Introduction

The Morita–Baylis–Hillman (MBH) reaction[1,2] has emerged in recent years as an attractive strategy for the quick generation of multifunctional molecules and as a key step in syntheses of complex bioactive natural products and designed molecules.[3] The method involves introduction of a substituent at the α-position of an activated alkene in a one-pot, room-temperature, and atom-economical fashion through the Lewis base mediated reaction between an activated alkene and a carbon- or heteroatom-centered electrophile.[4] Various activated alkenes such as enones, enals, acrylates, acrylamides, acrylonitrile, and vinyl sulfoxides/sulfones/sulfonates/phosphonates, as well as electrophiles such as aldehydes, activated ketones/imines/alkenes/azo compounds, and iminium salts have been successfully employed in MBH reactions.[3]

Numerous amines, phosphanes, and other nucleophilic Lewis bases have been found to catalyze MBH reactions.[3] Substantial rate acceleration for this eminently sluggish reaction has been achieved through addition of co-catalysts and application of new reaction media and conditions.[5] Recent successes in the intramolecular[6] and asymmetric[7] versions of this reaction has further transformed it into a reaction of exceptional topical interest.

Although several activated alkenes, as mentioned above, have been employed as substrates in MBH reactions, conjugated nitroalkenes have not received much attention until recently. This is despite the fact that Baylis and Hillman, in their patent, reported the synthesis of α-hydroxyethylated nitroethylene through the reaction between nitroethylene and acetaldehyde in the presence of DABCO.[2] The fact that the superior Michael acceptor abilities of nitroalkenes have been extensively investigated in recent decades[8,9] – and that the first step in the MBH reaction is the Michael-type addition of the catalyst[4] – has also not evoked sufficient interest for nitroalkenes to have become widely employed as substrates in MBH reactions.

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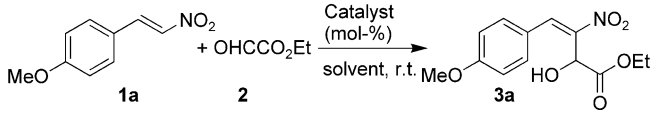
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900475.

In the above scenario, our endeavors to achieve reactions between nitroalkenes and various electrophiles such as formaldehyde,[10–11] activated carbonyl compounds[12]/imines[13]/alkenes,[14] and azodicarboxylates[15] in the presence of imidazole or DMAP as the catalyst have met with success in recent years. The anti-cancer activities exhibited by many MBH adducts of nitroalkenes at low micromolar concentrations, through targeting of tubulins/microtubules,[11,13,14] and the potential application of MBH adducts as valuable intermediates in the synthesis of amino alcohols, amino acids, and heterocycles encouraged us to expand the scope of the MBH reaction by introducing aliphatic nitroalkenes and aromatic nitrodienes as substrates for the first time. This report is the full version of our preliminary communication relating to the reactions between aromatic nitroalkenes and various activated non-enolizable carbonyl compounds.[12] The well-documented reactivities of activated aldehydes[16] and activated ketones[17–19] as electrophiles with various activated alkenes such as vinyl ketones, acrylates, and acrylonitrile also encouraged us to investigate the reactivities of such electrophiles with conjugated nitroalkenes in detail.

Results and Discussion

Reactions between various carbonyl electrophiles and aromatic or heteroaromatic nitroalkenes were investigated by initially taking 4-methoxy-α-nitrostyrene (**1a**) as the model substrate and ethyl glyoxylate (**2**) as the model electrophile (Scheme 1).



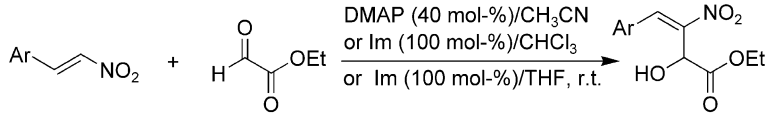
Scheme 1.

Our optimization studies suggested that both DMAP (40 mol-%) and imidazole (100 mol-%) would be suitable catalysts for this reaction.[12] Whereas acetonitrile was found to be the best solvent for the DMAP-catalyzed reaction, both chloroform and THF were suitable for the imidazole-catalyzed reaction.

It is important to note that, whereas the DMAP-catalyzed reactions required only ≤30 min for completion, the imidazole-catalyzed reactions were slower, requiring up to 48 h (Table 1). In general, aromatic nitroalkenes **1a**–**e** reacted with ethyl glyoxylate (**2**) to provide the MBH adducts **3a**–**e** in excellent yields under all conditions tested (Entries 1–5), particularly with DMAP as the catalyst [Entries 1(a)–5(a), Table 1]. Whereas the yields of MBH adducts **3h**–**i** derived from nitroalkenes **1h**–**i** were low to moderate under all three sets of conditions (Entries 8–9), other aromatic (**1f**–**g** and **1j**–**l**, Entries 6–7 and 10–12, respectively) and heteroaromatic (**1n**–**r**, Entries 13–17) nitroalkenes delivered the MBH adducts in moderate to good yields (Table 1).

The *E* geometries of the glyoxylate adducts **3** were confirmed by detailed NMR analysis and X-ray crystallogra-

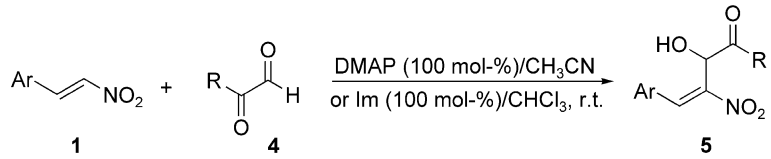
Table 1. MBH reactions between nitroalkenes **1a**–**r** and ethyl glyoxylate (**2**)[a] in the presence variously of DMAP in CH_3CN or of imidazole in $CHCl_3$ or THF at room temperature.



Entry	1	Ar	DMAP/CH_3CN (a)		Imidazole/$CHCl_3$ (b)		Imidazole/THF (c)	
			Time	Yield [%][b]	Time	Yield [%][b]	Time	Yield [%][b]
1	**a**	4-$MeOC_6H_4$	10 min	81	3 h	73	16 h	68
2	**b**	2,4-$(MeO)_2C_6H_3$	5 min	95	13 h	80	33 h	70
3	**c**	2,5-$(MeO)_2C_6H_3$	5 min	99	7 h	78	30 h	71
4	**d**	4-$Me_2NC_6H_4$	20 min	98	24 h	83	36 h	80
5	**e**	3,4-$(MeO)_2C_6H_3$	10 min	89	7 h	72	14 h	65
6	**f**	3,4-$(OCH_2O)C_6H_3$	15 min	65	10 h	50	24 h	50
7	**g**	3-MeO-4-HOC_6H_3	10 min	60	30 h	49	48 h	40
8	**h**	4-ClC_6H_4	15 min	45	24 h	38	40 h	43
9	**i**	Ph	30 min	33	5 h	31	21 h	25
10	**j**	2-propargyloxyC_6H_4	15 min	52	2 h	52	23 h	48
11	**k**	2-allyloxyC_6H_4	20 min	69	2 h	62	25 h	53
12	**l**	3,4,5-$(OMe)_3C_6H_2$	10 min	90	8 h	65	20 h	55
13	**n**	2-furyl	5 min	63	7 h	67	25 h	65
14	**o**	2-thienyl	5 min	64	6 h	68	30 h	65
15	**p**	3-furyl	10 min	60	6 h	60	5 h	55
16	**q**	3-thienyl	20 min	60	6 h	68	8 h	76
17	**r**	3-indolyl	30 min	65	8 h	55	15 h	48

[a] 4 equiv. as 50% solutions in toluene both for DMAP- and for imidazole-catalyzed reactions. [b] Isolated yields of **3** after silica gel column chromatography. The low to moderate yields in some cases are presumably due to polymerization of nitroalkenes. No other side reactions were observed in any of the cases.

Table 2. MBH reactions between nitroalkenes **1** and aldehydes **4a**–**c**[a] in the presence either of DMAP in CH_3CN or of imidazole in $CHCl_3$ at room temperature.



1 **4** **5**

Entry	**1**	Ar	**4**	R	**5**	DMAP/CH_3CN (a)		Imidazole/THF (b)	
						Time	Yield [%][b]	Time	Yield [%][b]
1	**a**	4-$MeOC_6H_4$	**a**	H	**a**	7 d	–	7 d	–
2	**a**	4-$MeOC_6H_4$	**b**	CH_3	**b**	2 d	26 (50)	2 d	20 (52)
3	**b**	2,4-$(MeO)_2C_6H_3$	**b**	CH_3	**c**	2 d	32 (50)	2 d	30 (35)
4	**c**	2,5-$(MeO)_2C_6H_3$	**b**	CH_3	**d**	2 d	30 (40)	2 d	28 (30)
5	**n**	2-furyl	**b**	CH_3	**e**	2 d	33 (40)	2 d	25 (45)
6	**p**	3-furyl	**b**	CH_3	**f**	2 d	35 (25)	2 d	36 (35)
7	**a**	4-$MeOC_6H_4$	**c**	Ph	**g**	7 d	–	7 d	–

[a] 4 equiv. for both DMAP- and imidazole-catalyzed reactions. [b] Isolated yields of **5** after silica gel column chromatography; amount (%) of recovered **1** in parentheses.

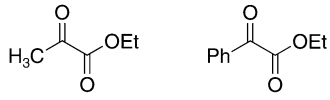
phy. In general, for compounds **3a**–**l** and **3n**–**r**, the styrenic protons appeared as singlets in the δ = 8.00–8.70 ppm range (Table S1, Supporting Information). Further, the NOE interaction between the aromatic protons and the CH part of the CHOH group and the absence of any such interaction between the styrenic proton and the CHOH group or the Et group in the representative compound **3d** was indicative of the *E* geometries of the styrenic double bonds in compounds **3**. The structure and stereochemistry were further unambiguously established by a single-crystal X-ray diffraction analysis of **3d**.[12]

The above reaction conditions were also applied, with minor modifications, to MBH reactions between nitroalkenes and other activated carbonyl compounds. Reactions between various aromatic (**1a**–**c**) or heteroaromatic (**1n**–**p**) nitroalkenes and activated aldehydes such as glyoxal (**4a**), pyruvaldehyde (**4b**), and phenylglyoxal (**4c**) were therefore investigated (Table 2). Interestingly, whereas glyoxal (**4a**) and phenylglyoxal (**4c**) remained unreactive even after 7 d (Entries 1 and 7), pyruvaldehyde (**4b**) reacted with aromatic nitroalkenes **1a**–**c** and heteroaromatic ones **1n**–**p** to afford the MBH adducts **5b**–**f** in low to moderate yields (Table 2).

Although substantial amounts of nitroalkenes were recovered from these reactions, the possible application of pyruvaldehyde (**4b**) as an electrophile in the MBH reaction has to the best of our knowledge been demonstrated here for the first time.[20]

The *E* geometries of the double bonds in the MBH adducts **5b**–**f** were confirmed by correlating the ^1H NMR chemical shifts of the styrenic protons with those of compounds **3**. As in the case of **3**, the styrenic protons in **5b**–**f** appeared as singlets in the δ = 8.00–8.60 ppm range (Table S2, Supporting Information).

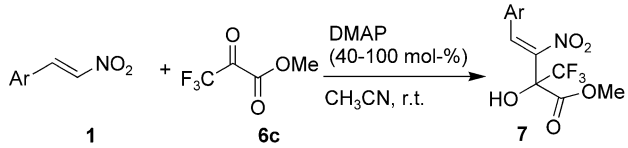
Our attempts to obtain reactions between oxo esters – namely, pyruvate **6a** and phenylglyoxylate **6b** (Figure 1) – and various nitroalkenes in the presence of DMAP or imidazole as catalyst were unsuccessful. However, we were pleased to observe the formation of MBH adducts **7a**–**d** when trifluoropyruvate **6c** was treated with various aromatic (**1a**, **1c**–**d**) and heteroaromatic (**1p**) nitroalkenes in the presence of DMAP as the catalyst (Table 3). Although low yields and prolonged reaction times were encountered when only 40 mol-% of DMAP was used as the catalyst (Entry 1, Table 3), increasing of the amount of the catalyst to 100 mol-% not only reduced the reaction times, but also substantially improved the yields (Entries 1–4).



6a **6b**

Figure 1. α-Oxo esters.

Table 3. MBH reactions between nitroalkenes **1** and oxo ester **6c**[a] in the presence of DMAP in CH_3CN at room temperature.



1 **6c** **7**

Entry	**1**	Ar	**7**	DMAP/CH_3CN	
				Time	Yield [%][b]
1	**a**	4-$MeOC_6H_4$	**a**	2 d	40[c]
				3 h	70[d]
2	**c**	2,5-$(MeO)_2C_6H_3$	**b**	4 h	71[d]
3	**d**	4-$Me_2NC_6H_4$	**c**	10 h	80[d,e]
4	**p**	3-furyl	**d**	30 min	63[d]

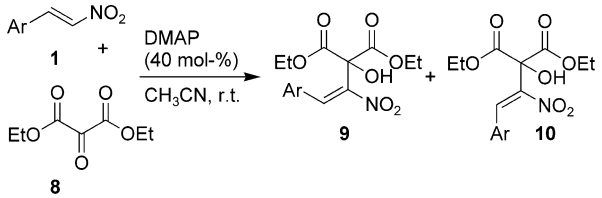
[a] 4 equiv. [b] Isolated yields of **7a**–**d** after silica gel column chromatography. [c] 40% of DMAP was used. [d] 100% of DMAP was used. [e] 5% of **1d** was recovered.

Unlike in the cases of the glyoxylate adducts **3** and the pyruvaldehyde adducts **5**, the styrenic protons of which resonated in the δ = 8.00–8.70 ppm range, the styrenic protons of the MBH adducts of trifluoropyruvates **7a**–**d** were relatively shielded (δ = 7.20–7.90 ppm, Table S3, Supporting In-

formation), suggesting that the geometries of their styrenic double bonds could be *Z*. This was confirmed by a single-crystal X-ray analysis of the representative compound **7c** (Table S4, Supporting Information).[21]

Treatment of various nitroalkenes with a ketone activated by two ester groups – namely, oxomalonate **8** – in the presence of DMAP as the catalyst led to the formation of the MBH adducts **9**–**10** in moderate to good yields (Table 4). These reactions were complete in 20 min, and in some cases the products were single *E* isomers (Entries 1, 3, and 4) and in other cases mixtures of *E* and *Z* isomers with preferences for the former (Entries 2 and 5, Table 4). The fact that that the major or the exclusive isomers could be the *E* isomers was verified by comparison of the ^{1}H NMR chemical shifts of the styrenic protons (Table S5, Supporting Information). This was further corroborated by a single-crystal X-ray analysis of the representative compound **9a** (Table S6, Supporting Information).

Table 4. MBH reactions between nitroalkenes **1** and diethyl oxomalonate (**8a**) at room temperature in the presence of DMAP in CH_3CN.



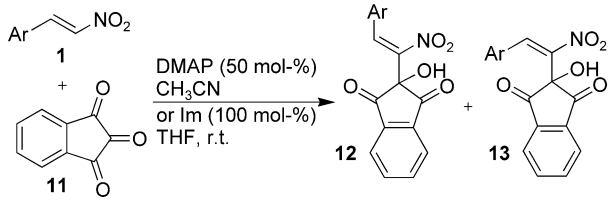
Entry	1	Ar	9/10	DMAP/CH_3CN Time	Yield [%][b] (9/10)
1	**a**	4-$MeOC_6H_4$	**a**	20 min	85 (100:0)
2	**d**	4-$Me_2NC_6H_4$	**b**	20 min	55 (78:22)
3	**e**	3,4-$(MeO)_2C_6H_3$	**c**	20 min	65 (100:0)
4	**l**	3,4,5-$(MeO)_3C_6H_2$	**d**	20 min	43 (100:0)
5	**n**	2-furyl	**e**	20 min	53 (71:29)[c]

[a] 4 equiv. [b] Isolated yield of **9** + **10** after silica gel column chromatography. The diastereomeric ratios of products **9** and **10** were determined by ^{1}H NMR spectroscopy. The moderate yields in some cases are presumably due to polymerization of nitroalkenes. No other side reactions were observed in any cases. [c] Inseparable mixture.

Having succeeded in obtaining reactions between various nitroalkenes and open-chain multi-carbonyl compounds as electrophiles, we turned our attention to cyclic multi-carbonyl compounds in anticipation that the strain inherent in such compounds should make them react with nitroalkenes under the MBH conditions. We therefore examined the electrophilicity of ninhydrin (**11**), and we were pleased to isolate the MBH adducts **12** and **13** in good yields in most cases (Table 5). As in the reactions between nitroalkenes **1** and glyoxylate **2** (Table 1), the reactions between **1** and ninhydrin (**11**) were catalyzed both by DMAP and by imidazole. As before, the DMAP-catalyzed reactions were also faster in this case, providing the products in moderate to good yields in ≤30 min [Entries 1(a)–9(a), Table 5]. On the other hand, the imidazole-catalyzed reactions required 5–22 h for completion. Nevertheless, greater selectivities in favor of the *E* isomers were in many cases observed in the imidazole-catalyzed reactions (Entries 1–3, 5 and 9, Table 5).

Clear distinctions between the *Z* isomers **12** and the *E* isomers **13** could be made on the basis of their IR, ^{1}H NMR, and ^{13}C NMR characteristics. First of all, the IR peaks for the OH groups in the *Z* isomers in general appeared at higher frequencies (3404–3434 cm^{-1}) than those in the *E* isomers (3125–3370 cm^{-1}, Supporting Information). The general chemical shift range observed for the styrenic protons in the

Table 5. MBH reactions between nitroalkenes **1** and ninhydrin (**11**)[a] in the presence of DMAP in CH_3CN and imidazole in THF at room temperature.



Entry	1	Ar	DMAP/CH_3CN (a) Time	Yield [%][b] (12/13)	Imidazole/$CHCl_3$ (b) Time	Yield [%][b] (12/13)
1	**a**	4-$MeOC_6H_4$	15 min	64 (55:45)	22 h	63 (69:31)[c]
2	**d**	4-$Me_2NC_6H_4$	2 h	53 (65:35)	24 h	56 (79:21)[c]
3	**h**	4-ClC_6H_4	15 min	43 (62:38)	20 h	55 (67:33)
4	**i**	Ph	15 min	49 (67:33)	16 h	59 (64:36)[c]
5	**k**	2-allyloxyC_6H_4	30 min	71 (59:41)	9 h	68 (63:37)
6	**m**	2-$O_2NC_6H_4$	15 min	75 (100:0)	6 h	79 (100:0)
7	**n**	2-furyl	30 min	78 (100:0)	5 h	73 (100:0)
8	**o**	2-thienyl	30 min	72 (100:0)	6 h	75 (100:0)
9	**p**	3-furyl	30 min	64 (56:44)	5 h	67 (69:31)

[a] 3 equiv. for both DMAP- and imidazole-catalyzed reactions. [b] Isolated yield of **12** + **13** after purification by silica gel column chromatography. The diastereomeric ratio of **12** and **13** was determined by ^{1}H NMR spectroscopy. The moderate yields in some cases are presumably due to polymerization of nitroalkenes. No other side reactions were observed in any of the cases. [c] Inseparable mixture.

^{1}H NMR spectra of the *Z* isomers was δ = 7.54–8.18 ppm, whereas for the *E* isomers it was δ = 8.50–8.91 ppm (Table S7, Supporting Information). In the ^{13}C NMR spectra, the CHOH carbon atoms of the *Z* isomers resonated at higher field (δ = 75.9–76.9 ppm) than those of the *E* isomers (δ = 76.9–78.3 ppm, Supporting Information). Since ^{1}H,^{1}H 2D-NOESY experiments did not provide satisfactory results, the above assignment was unambiguously supported by a single-crystal X-ray analysis of the representative system **12p**.[12]

Encouraged by the results obtained from the reactions between β-aryl- and β-heteroaryl-nitroethylenes and various carbonyl electrophiles such as glyoxylate **2**, pyruvaldehyde (**4b**), trifluoropyruvate **6c**, oxomalonate **8** and ninhydrin (**11**), we decided to investigate the reactivities of selected β-alkyl-nitroethylenes **14a**–**d** (Figure 2) with some of these electrophiles.

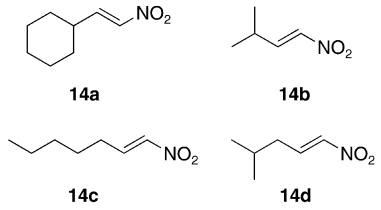


Figure 2. Aliphatic nitroalkenes.

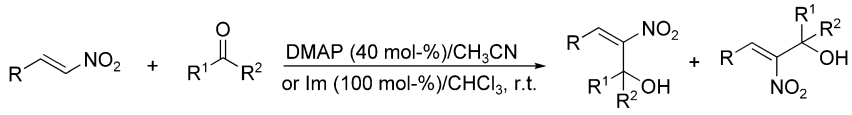
Initially, **14a** and **14b** were screened for their reactivities towards these electrophiles, as well as towards the smallest carbonyl electrophile, formaldehyde (**15**, Table 6). Needless to mention, the nitroalkenes **14a** and **14b** exhibited similar reactivities towards the electrophiles we screened. Treatment of **14a** or **14b** with glyoxylate **2**, for instance, provided the *E* isomers **16a** and **16e** of the MBH adducts as the major or exclusive products (Entries 1 and 5, Table 6), as in the case of the aromatic nitroalkenes **1** (see Table 1).

The comparable chemical shifts (δ = 7.10 and 7.25 ppm) observed for the olefinic protons in **16a** and **16e**, together with the appearance of the olefinic proton signal in the minor isomer **17a** at δ = 5.95 ppm, suggested the *E* geometries for **16a** and **16e** (Table S1, Supporting Information). This was further confirmed by ^{1}H,^{1}H 1D-NOE examination of **16a**, in which irradiation of the CH in the CHOH group caused an NOE enhancement of 8.3% for the signal of the allylic proton on the cyclohexane ring (see the Supporting Information).

In contrast with the formation of *E* isomers in the reactions between **14a** or **14b** and glyoxylate **2**, the *Z* isomers **17b** and **17g** were the major or exclusive products in the reactions between **14a** or **14b** and trifluoropyruvate **6c** (Entries 2 and 7, Table 6). The selectivities observed in these cases were again consistent with those observed in the cases of aromatic nitroalkenes **1** (see Table 3, see also Table S3, Supporting Information, for correlation of the ^{1}H NMR chemical shifts of the β-H moieties). The structure of **17b** was confirmed by X-ray analysis (Table S8, Supporting Information).

The reactions between **14a** or **14b** and oxomalonate **8** (Entries 3 and 8, Table 6) exhibited selectivity opposite to that observed for the aromatic nitroalkenes **1** (see Table 4). The DMAP- and imidazole-catalyzed reactions between nitroalkene **14a** and oxomalonate **8** provided the MBH adducts **16c** + **17c** in 80% and 53% yields, respectively, with a common *E*/*Z* ratio of 28:72 (Entry 3, Table 6). The similar reactions between **14b** and **8** afforded the MBH adducts **16h** + **17h** in 75% and 66% yields, respectively, with a common *E*/*Z* ratio of 31:69 (Entry 8, Table 6). The *E* and *Z* geometries for the two isomers were assigned from the ^{1}H NMR chemical shifts of the key olefinic protons in the two isomers. Whereas in the minor *E* isomers **16c** and **16h**, the signals of the olefinic protons appeared at δ = 7.03 and

Table 6. MBH reactions between nitroalkenes **14a** or **14b** and various electrophiles[a] in the presence of DMAP in CH_3CN and imidazole in $CHCl_3$ at room temperature.



14a-b **2**, **4b**, **6c**, **8**, **15** **16** **17**

Entry	**14**	R	Electrophile	R^1	R^2	**16** + **17**	DMAP/CH_3CN (a) Time	DMAP/CH_3CN (a) Yield [%][b] (**16**/**17**)	Imidazole/$CHCl_3$ (b) Time	Imidazole/$CHCl_3$ (b) Yield [%][b] (**16**/**17**)
1	**a**	Cy	**2**	H	CO_2Et	**a**	5 min	88 (92:8)	15 min	45 (92:8)
2	**a**	Cy	**6c**	CF_3	CO_2Me	**b**	5 min	85 (3:97)	10 min	41 (3:97)
3	**a**	Cy	**8**	CO_2Et	CO_2Et	**c**	5 min	80 (28:72)[c]	10 min	53 (28:72)[c]
4	**a**	Cy	**15**	H	H	**d**	5 min	61 (91:9)[d]	24 h	–[e]
5	**b**	*i*Pr	**2**	H	CO_2Et	**e**	5 min	73 (100:0)[f]	10 min	55 (100:0)[f]
6	**b**	*i*Pr	**4b**	H	COMe	**f**	10 min	40 (87:13)[c]	15 min	35 (87:13)[c]
7	**b**	*i*Pr	**6c**	CF_3	CO_2Me	**g**	5 min	80 (0:100)	10 min	62 (0:100)
8	**b**	*i*Pr	**8**	CO_2Et	CO_2Et	**h**	5 min	75 (31:69)[c]	10 min	66 (31:69)[c]
9	**b**	*i*Pr	**15**	H	H	**i**	5 min	45 (88:12)	24 h	–[e]

[a] 4 equiv. for both DMAP- and imidazole-catalyzed reactions. [b] Isolated yield of **16** + **17** after silica gel column chromatography. The diastereomeric ratio of **16** and **17** was determined by ^{1}H NMR spectroscopy. The moderate yields observed in some cases are presumably due to polymerization of nitroalkenes. No other side reactions were observed in any of the cases. [c] Inseparable mixture. [d] The major isomer was isolated in pure form. [e] Complex mixture including substantial amount of starting material. [f] Crude **16e** was acetylated for the purpose of characterization, due to its instability.

6.98 ppm, respectively, in the major *Z* isomers **17c** and **17h** the signals of the olefinic protons appeared at δ = 6.15 and 6.14 ppm, respectively (Table S5, Supporting Information).

Reactions between nitroalkenes **14a** or **14b** and formaldehyde (**15**) were feasible only with DMAP as the catalyst (Entries 4a and 9a, Table 6). The MBH adducts **16d** + **17d** were isolated in 61% yield with an *E*/*Z* ratio of 91:9 (Entry 4a, Table 6). Similarly, **16i** + **17i** were isolated in moderate yield (45%) with an *E*/*Z* ratio of 88:12 (Entry 9a, Table 6). Surprisingly, the reactions between **14a** or **14b** and formaldehyde (**15**) under the imidazole-catalyzed conditions [Entries 4(b) and 9(b), Table 6] were not satisfactory. The *E* stereochemistries were assigned for **16d** and **16i** from the fact that the olefinic protons in these major isomers (δ = 7.09 and 7.05 ppm) were deshielded by ca. 1 ppm in relation to those in the minor isomers **17d** and **17i** (δ = 5.96 and 5.93 ppm, Table S9, Supporting Information).

Finally, the reaction between nitroalkene **14b** and pyruvaldehyde (**4b**) provided the MBH adducts **16f** + **17f** in moderate yield [40%, Method (a) and 35%, Method (b)] with an *E*/*Z* ratio of 87:13 (Entry 6, Table 6). The styrenic proton in the *E* isomer **16f** was deshielded by ca. 1.2 ppm relative to that in the *Z* isomer **17f** (Table S2, Supporting Information).

The products formed in the MBH reactions discussed so far possess the double bond in conjugation with the nitro group. Interestingly, in the reactions between aliphatic nitroalkenes possessing γ-methylene groups, such as **14c** or **14d**, and oxomalonate **8**, the β,γ-unsaturated nitro compounds **18a** and **18b** were isolated instead of the expected α,β-unsaturated nitro compounds (Table 7). This was confirmed by ^{1}H, ^{13}C, and ^{13}C-DEPT spectra (see the Supporting Information). Whereas the signals of the α- and β-protons (with respect to the NO_2 group) overlapped (δ = 5.60–5.80 ppm) in the ^{1}H NMR spectra of **18a** and **18b**, the γ-H protons each appeared as a ddd at δ = 6.00 ppm. This was confirmed by a ^{1}H,^{1}H 2D-COSY experiment on **18b** (see the Supporting Information). Analysis of the ^{13}C NMR spectra of **18a** and **18b** with the aid of DEPT spectra further confirmed the above assignment in that the α-, β-, and γ-methine carbon atoms appear at δ = 90.4, 115.7 and 150.4 ppm, respectively, in **18a** and at δ = 90.4, 118.2 and 144.1 ppm, respectively, in **18b**. The geometries of the double bonds were confirmed to be *E* from the ^{1}H NMR spectra (*J* values for the olefinic protons of 12.8 Hz in **18a** and 11.4 Hz in **18b**).

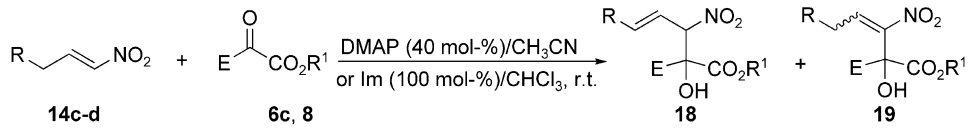
It appears that the formation of unusual products of type **18a** or **18b** is observed only when oxomalonate **8** is used as the electrophile. For instance, when trifluoropyruvate **6c** was treated with nitroalkene **14d** under DMAP-catalyzed conditions, the only product isolated was the MBH adduct **19c**, albeit in low yield (37%, Entry 3, Table 7).

The formation of β,γ-unsaturated nitro compounds **18a** or **18b** instead of the expected MBH adducts **19a** or **19b** in the reactions between nitroalkenes **14c** or **14d** and oxomalonate **8** (Entries 1–2, Table 7) can be interpreted in terms of the two elimination pathways available to the zwitterionic intermediate arising from addition of nitronate **I** to the electrophile **8** (Scheme 2). If the intermediate were to undergo elimination through α-hydrogen abstraction by the alkoxides, as shown in **II**, the product formed would be the α,β-unsaturated compound **19**, which is not observed.[22] On the other hand, elimination through γ-hydrogen abstraction by the alkoxide as shown in **III** would result in the β,γ-unsaturated nitro compound **18**, which is the only product isolated. It is proposed that the γ-hydrogen abstraction by the alkoxide as shown in **III** is facilitated by the chair-like conformation adopted by **III**. Although such a chair-like conformation might also be possible for the zwitterionic intermediates arising from **14a** or **14b**, such a conformation is either destabilized due to 1,3-diaxial interaction as in **IV** or the γ-hydrogen atom is not appropriately oriented to undergo abstraction by the alkoxide as in **V** (Scheme 3).

Subsequent to our studies on the MBH reactions between aromatic, heteroaromatic, or aliphatic nitroalkenes and various carbonyl electrophiles, similar reactions between the nitrodienes **20a**–**c** (Figure 3),[23] prepared through Henry reactions of substituted cinnamaldehydes, and selected electrophiles such as glyoxylate **2**, trifluoropyruvate **6c**, and formaldehyde (**15**) were investigated (Table 8).

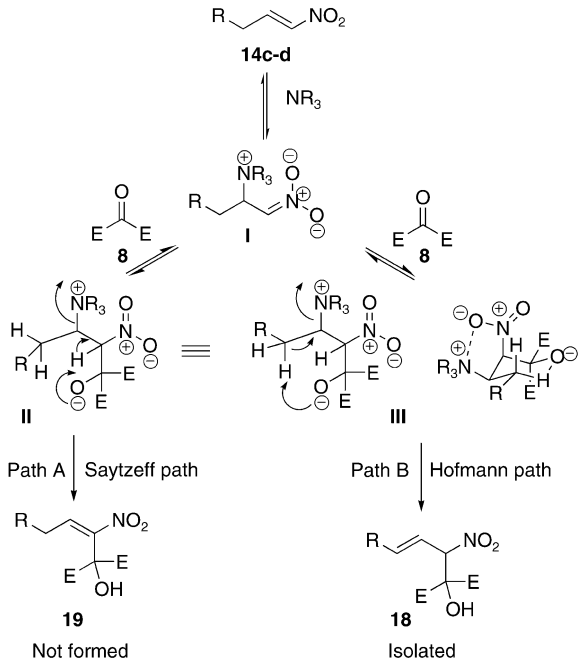
As observed in previous instances, the DMAP-catalyzed reactions were much faster than the imidazole-catalyzed reactions and provided the products in better yields, but there

Table 7. MBH reactions of nitroalkenes **14c** or **14d** and oxomalonate **8**[a] in the presence of DMAP in CH_3CN and imidazole in $CHCl_3$ at room temperature.

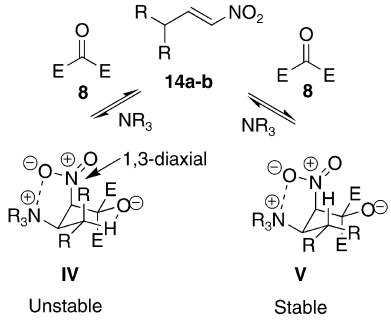


Entry	**14**	R	**6c**, **8**	E, R^1	**18/19**	DMAP/CH_3CN (a)		Imidazole/$CHCl_3$ (b)	
						Time	Yield [%][b] (**18**/**19**)	Time	Yield [%][b] (**18**/**19**)
1	**c**	*i*Pr	**8**	CO_2Et, Et	**a**	5 min	45 (100:0)	5 min	40 (100:0)
2	**d**	*n*Pent	**8**	CO_2Et, Et	**b**	5 min	57 (100:0)	5 min	48 (100:0)
3	**d**	*n*Pent	**6c**	CF_3, Me	**c**	45 min	37 (0:100)[c]	–	–[d]

[a] 4 equiv. for both DMAP- and imidazole-catalyzed reactions. [b] Isolated yield of **18** after silica gel column chromatography. The moderate yields are presumably due to polymerization of nitroalkenes. No other side reactions were observed. [c] *Z* isomer. [d] No reaction.



Scheme 2.



Scheme 3.

was no appreciable change in the selectivity. Whereas treatment of nitrodienes **20a**–**c** with glyoxylate **2** provided the MBH adducts **21**/**22a**–**c** in 80–88% yields in 20–30 min under the DMAP-catalyzed conditions [Entries 1(a)–3(a)], for the imidazole-catalyzed reactions the yields were moderate (60–68%), and they required 5–12 h to go to completion [Entries 1(b)–3(b), Table 8].

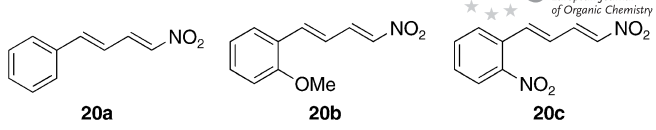
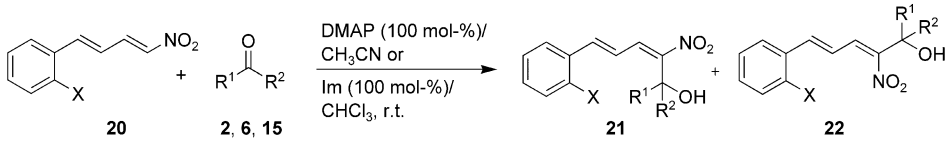


Figure 3. Aromatic nitrodienes.

With regard to the stereochemistries of **21**/**22a**–**c**, the chemical shifts and coupling constants of the hydrogen atoms α, β, and γ with respect to the nitro groups in the dienic moieties were analyzed. The appearance of the signals of the β-protons in **21a**–**c** in the δ = 7.95–8.00 ppm range suggested that the α,β-double bonds have *E* configurations (Table S1 in the Supporting Information). Vicinal coupling constants of J = 11–12 Hz for the couplings between α-H and β-H in **21a**–**c** further confirmed this assignment. That the γ,δ-double bonds are also *E* is evident from the vicinal couplings between γ-H and δ-H, with J values of 11.9 Hz in **21a**, 15.3 Hz in **21b**, and 15.4 Hz in **21c**. This was further supported by a ^{1}H,^{1}H 2D-NOESY experiment on the representative compound **21a**, in that a strong NOE was observed between the CH part of the CHOH group and the γ-H (see the Supporting Information).

As in the cases of aromatic, heteroaromatic, and aliphatic nitroalkenes, the reaction between nitrodiene **20a** and trifluoropyruvate **6** provided the *Z* isomer as the exclusive product in high yield both under the DMAP- and under the imidazole-catalyzed conditions (Entry 4, Table 8). The *Z* configuration was assigned to **22d** on the basis of correlation of the ^{1}H NMR chemical shift of β-H (δ = 7.60 ppm) with those in the similar adducts **7a**–**c** and **7e** (δ = 7.22–7.85 ppm, Table S3, Supporting Information). The structure of **22d** was further unambiguously established by X-ray analysis (Table S10, Supporting Information).

Table 8. MBH reactions between nitrodienes **20** and various electrophiles[a] in the presence of DMAP in acetonitrile or imidazole in chloroform at room temperature.

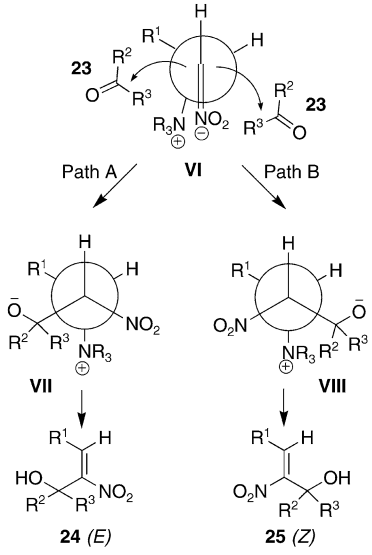


Entry	**20**	X	**2**, **6**, **15**	R^1, R^2	**21**/**22**	DMAP/CH_3CN (a) Time	DMAP/CH_3CN (a) Yield[b] [%] (**21**/**22**)	Imidazole/$CHCl_3$ (b) Time	Imidazole/$CHCl_3$ (b) Yield [%][b] (**21**/**22**)
1	**a**	H	**2**	H, CO_2Et	**a**	30 min	85 (100:0)	5 h	60 (100:0)
2	**b**	OMe	**2**	H, CO_2Et	**b**	30 min	88 (92:8)	7 h	63 (90:10)
3	**c**	NO_2	**2**	H, CO_2Et	**c**	40 min	80 (100:0)	12 h	68 (100:0)
4	**a**	H	**6**	CF_3, CO_2Me	**d**	20 min	78 (0:100)	2 h	79 (0:100)
5	**a**	H	**15**	H, H	**e**	45 min	70 (100:0)	16 h	50 (100:0)[c]
6	**b**	OMe	**15**	H, H	**f**	45 min	63 (100:0)	16 h	53 (100:0)[c]

[a] 4 equiv. for both DMAP- and imidazole-catalyzed reactions. [b] Isolated yields of **21** and **22** after silica gel column chromatography. The diastereomeric ratio of **21** and **22** was determined by ^{1}H NMR spectroscopy. The moderate yields observed in some cases are presumably due to polymerization of nitroalkenes. No other side reactions were observed in any of the cases. [c] Solvent was THF.

Finally, the reactions between nitrodienes **20a** or **20b** and formaldehyde (**15**) proceeded well under both DMAP- and imidazole-catalyzed conditions (Entries 5–6, Table 8). The stereochemistries of the α-hydroxymethylated nitrodienes **21e** and **21f** were confirmed by correlation of the ^{1}H NMR chemical shifts of the β-protons with those in similar adducts (Table S9, Supporting Information).[24]

In the reactions between various nitroalkenes or nitrodienes and electrophiles such as glyoxylate **2**, pyruvaldehyde (**4b**), or formaldehyde (**15**), in which R^2 and/or R^3 are/is H, the *E* isomers **24** are the major or exclusive products (Scheme 4). On the other hand, the *Z* isomers **25** are the major or exclusive products in the corresponding reactions with electrophiles such as trifluoropyruvate **6c** and ninhydrin **11c** in which R^2 and $R^3 \neq$ H. The only exception is oxomalonate **8**, which exhibited opposite selectivities with aromatic and aliphatic nitroalkenes, in that, whereas *E* isomers are favored for aromatic and heteroaromatic nitroalkenes, *Z* isomers are the major products in cases of aliphatic nitroalkenes (see Tables 4 and 6). The above selectivities can be explained on the basis of the approach of the electrophile from the two faces of the nitronate **VI** and the relative stabilities of the products **24** and **25** (Scheme 4).



Scheme 4.

It turns out that approach of the electrophile **23** from the hindered side (path A) is tolerated if there is no severe steric interaction (i.e., when R^2 and/or R^3 are/is H) between the alkoxide and the β-substituent (R^1) in the transition state leading to intermediate **VII** and product **24** (*E* isomer). Alternatively, path B, involving approach of the electrophile **23** from the less hindered side, is favored when R^2 and R^3 are not H. This approach avoids any possible steric interaction between the alkoxide and the β-substituent (R^1) in the transition state leading to intermediate **VIII** and product **25** (*Z* isomer). In the case of oxomalonate **8**, the *E* isomer **24** is favored (path A) for aromatic nitroalkenes (R^1 = Ar), presumably because the planar aromatic ring in nitronate **VI** does not exert any severe steric hindrance on the approaching electrophile **23** ($R^2 = R^3 = CO_2Et$), nor on the alkoxide group in **VII**. In contrast, the aliphatic substituent (R^1 = alkyl), by virtue of its spatial disposition, offers greater resistance to the approaching electrophile **23**, and path B leading to the *Z* isomer **25** is therefore favored.

The superior catalytic roles of DMAP[25] and imidazole[26] in the reactions between nitroalkenes or nitrodienes and various carbonyl electrophiles are amply evident from our experiments. Other amine and phosphane catalysts that have been and continue to be routinely employed in MBH reactions of various activated alkenes[3] were not effective in the case of nitroalkenes. It is interesting to note that, whereas imidazole, with a pK_a of 7.0, and DMAP, with a pK_a of 9.7, are good catalysts in our reactions, trimethylphosphane (TMP) and DABCO, with intermediate pK_a values (8.7 each), and DBU and tetramethylguanidine (TMG), with higher pK_a values (12.0 and 13.6, respectively), are not suitable for our reactions (Figure 4). This suggests that the catalytic activities of these nucleophilic Lewis bases do not correlate with their basicities.[27]

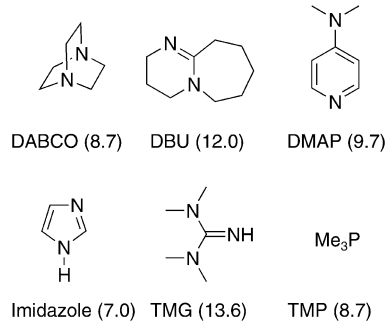
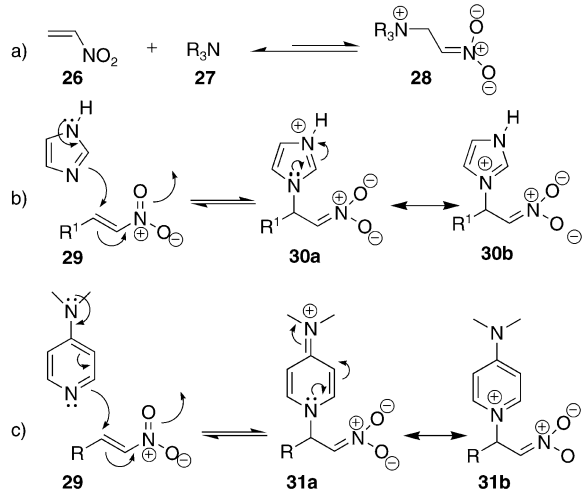


Figure 4. Commonly employed MBH catalysts and their pK_a values.

The above observation encouraged us to implicate the relative steric requirements of nucleophilic Lewis bases in their conjugate additions to β-substituted nitroalkenes and the relative stabilities of the zwitterionic intermediates arising from such addition. It has been reported that conjugate additions of amines to nitroalkenes are reversible (Scheme 5a).[28,29] Because MBH reactions are equilibrium-controlled, the reversibility in the first step is a major impediment that makes certain catalysts such as DABCO ineffective. However, the zwitterionic intermediates **30a/30b** or **31a/31b** arising from initial conjugate addition of imidazole or DMAP are resonance-stabilized and therefore less prone to undergo reverse reaction (Scheme 5b,c). It is important to note that the positive charge on the amine nitrogen atom is stabilized without violating the aromaticity of the imidazole moiety in **30a** or **30b**, or of the DMAP moiety in one of the contributing structures (**31b**).

Another important feature of the MBH reactions of nitroalkenes is that β-substituents do not inhibit the reaction. This is in stark contrast with the behavior of other activated alkenes containing β-substituents, which either do not react or react very sluggishly.[3] The fact that the reactions between nitroalkenes and most of the carbonyl electrophiles reported here take place in less than 60 min, particularly



Scheme 5.

under the DMAP-catalyzed conditions, suggests superior reactivities of nitroalkenes as MBH substrates vis-à-vis other activated alkenes. Our investigations of the possible reactivity of the parent nitroethylene with various electrophiles under controlled conditions will be reported in due course.

Conclusions

The reactivities of conjugated nitroalkenes, both aromatic and aliphatic, and nitrodienes with various carbonyl electrophiles under the Morita–Baylis–Hillman conditions have been thoroughly investigated. The studies have shown that aldehydes such as glyoxylate and pyruvaldehyde, as well as formaldehyde, oxo esters such as trifluoropyruvate and oxomalonate, and a cyclic polycarbonyl compound such as ninhydrin, are suitable electrophiles for the α-hydroxyalkylation of nitroalkenes and nitrodienes. Quite remarkably, DMAP and imidazole are the only two nucleophilic Lewis bases that were found to catalyze this reaction, presumably because of the smaller steric requirement and, more importantly, the resonance stabilization of the zwitterionic intermediates arising from the Michael-type additions of these catalysts. Formation of *E* and *Z* isomers of the MBH adducts with preference for *E* isomers was observed when R^1 and/or R^2 of the electrophile (R^1COR^2) was H and with preference for *Z* isomers when R^1 and $R^2 \neq H$. Unusual γ-hydrogen abstractions in the elimination step, leading to the formation of α-hydroxyalkylated β,γ-nitroalkenes, were observed in the reactions between oxomalonate and nitroalkenes possessing γ-CH_2 groups.

Experimental Section

General methods are provided in the Supporting Information.

DMAP-Catalyzed MBH Reactions of Nitroalkenes (Procedure A): DMAP (25 mg, 40 mol-% or 62.5 mg, 100 mol-%) was added to a stirred solution of the nitroalkene **1** (0.5 mmol) in MeCN (1 mL), followed by the activated carbonyl compound **2** (4 equiv.), and the reaction mixture was stirred at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (5 mL), the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography by elution with EtOAc/hextroalkenes (Procedure B): Imidazole (34 mg, 100 mol-%) was added to a stirred solution of the nitroalkene **1** (0.5 mmol) in dry $CHCl_3$ or THF (1 mL), followed by the activated carbonyl compound **2**, and the reaction mixture was stirred at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with water (5 mL), the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography by elution with EtOAc/hexane (gradient elution).

Representative experimental data (see the Supporting Information for complete data).[30]

Diethyl (*E*)-2-Hydroxy-2-[2-(4-methoxyphenyl)-1-nitrovinyl]malonate (9a): Yellow crystalline solid. Yield 150 mg (85%). m.p. 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (t, J = 7.1 Hz, 6 H), 3.85 (s, 3 H), 3.96 (ABqd, J = 10.8, 7.1 Hz, 4 H), 4.76 (s, 1 H), 6.94 (dd, J = 6.8, 2.2 Hz, 2 H), 7.51 (dd, J = 6.8, 2.2 Hz, 2 H), 8.31 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 55.4, 63.6, 77.4, 114.2, 123.1, 132.0, 140.3, 145.7, 162.0, 167.4 ppm. IR (film): $\tilde{\nu}$ = 3465 (br. m), 2979 (w), 1761 (s), 1639 (m), 160 (s), 1515 (m), 1322 (m), 1264 (s), 1140 (m) cm^{-1}. MS (70 eV): *m*/*z* (%) = 376 (50) [M + Na]$^+$, 342 (100), 336 (30). HRMS (70 eV) calcd. for $C_{16}H_{19}NO_8Na$ [M + Na]$^+$ 376.1008; found 376.1005.

Selected X-ray Data for 9a (CCDC-728134): $C_{16}H_{19}NO_8$, M = 353.32, triclinic, space group $P\bar{1}$, a = 6.798(2) Å, b = 10.1396(14) Å, c = 12.700(5) Å, α = 74.61(7), β = 85.56(3), γ = 79.315(18)°, V = 829.0(6) Å^3, D_c = 1.415 Mg m^{-3}, Z = 2, F(000) = 372, λ = 0.71073 Å, μ = 8.152 mm^{-1}. Total/unique reflections = 10056/4175 [R(int) = 0.0306], T = 293(2) K, θ range = 3.08–30.12°. Final R [$I > 2\sigma(I)$]: $R1$ = 0.0354, $wR2$ = 0.0718; R (all data): $R1$ = 0.0916, $wR2$ = 0.0791.

Methyl (*E*)-4-Cyclohexyl-2-hydroxy-3-nitro-2-(trifluoromethyl)but-3-enoate (16b) and Methyl (*Z*)-4-Cyclohexyl-2-hydroxy-3-nitro-2-(trifluoromethyl)but-3-enoate (17b): White crystalline solid. Yield 85% (132 mg) (3:97 ratio, Method A); 41% (64 mg) (3:97 ratio, Method B); major isomer **17b** (obtained in pure form by silica gel column chromatography of the mixture); m.p. 36–37 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.39 (m, 6 H), 1.68–1.79 (m, 4 H), 2.55–2.69 (m, 1 H), 3.97 (s, 3 H), 4.52 (s, 1 H), 6.20 (d, J = 9.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 24.9, 25.4, 31.3, 31.9, 38.0, 55.2, 76.37 (q, J = 31.3 Hz), 121.2 (q, J = 286.0 Hz), 140.7, 143.5, 167.4 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –74.7 ppm. IR (film): $\tilde{\nu}$ = 3434 (br. vs), 2934 (m), 2858 (w), 1757 (m), 1655 (m), 1541 (m), 1444 (w), 1364 (w), 1299 (m) cm^{-1}. MS (70 eV): *m*/*z* (%) = 334 (100) [M + Na]$^+$, 268 (35). HRMS (70 eV) calcd. for $C_{12}H_{16}F_3NO_5Na$ [M + Na]$^+$ 334.0878; found 334.0867.

Selected X-ray Data for 17b (CCDC-728136): $C_{12}H_{16}F_3NO_5$, M = 311.26, monoclinic, space group $P2_1/c$, a = 11.4463(7) Å, b = 12.3752(9) Å, c = 10.3759(7) Å, β = 102.057(6)°, V = 1437.33(17) Å^3, D_c = 1.438 Mg m^{-3}, Z = 4, F(000) = 648, λ = 0.71073 Å, μ = 0.135 mm^{-1}. Total/unique reflections = 6477/2490 [R(int) = 0.0494], T = 150(2) K, θ range = 3.29–24.99°. Final R

[$I > 2\sigma(I)$]: $R1$ = 0.0788, $wR2$ = 0.1569; R (all data): $R1$ = 0.1174, $wR2$ = 0.1729.

Methyl (3*Z*,5*E*)-2-Hydroxy-3-nitro-6-phenyl-2-(trifluoromethyl)-hexa-3,5-dienoate (22d): Yellow crystalline solid. Yield 78% (129 mg) (Method A), 79% (131 mg) (Method B); m.p. 122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 4.57 (br. s, 1 H), 7.05 (d, J = 10.9 Hz, 1 H), 7.17 (d, J = 15.6 Hz, 1 H), 7.39–7.40 (m, 3 H), 7.53–7.55 (m, 2 H), 7.60 (dd, J = 15.5, 10.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.1, 77.1 (q, J = 30.5 Hz), 120.7, 122.2 (q, J = 282.9 Hz), 128.2, 129.0, 130.7, 134.9, 135.6 (q, J = 2.3 Hz), 140.8, 148.3, 167.5 ppm. ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –74.1 ppm. IR (neat): $\tilde{\nu}$ = 3429 (br. vs), 2925 (w), 1748 (m), 1635 (s), 1529 (m), 1384 (m) cm^{-1}. MS (70 eV): *m*/*z* (%) = 332 (75) [M + H]$^+$, 264 (80), 254 (100). HRMS (70 eV) calcd. for $C_{14}H_{13}NO_5F_3$ [M + H]$^+$ 332.0746; found 332.0736.

Selected X-ray Data for 22d (CCDC-728135): $C_{28}H_{24}F_6N_2O_{10}$, M = 662.49, monoclinic, space group $P2_1/n$, a = 13.6872 (5) Å, b = 7.4396 (3) Å, c = 29.5302 (10) Å, β = 102.147(4)°, V = 2939.66(19) Å^3, D_c = 1.497 Mg m^{-3}, Z = 4, F(000) = 1360, λ = 0.71073 Å, μ = 0.137 mm^{-1}. Total/unique reflections = 19177/5161 [R(int) = 0.0221], T = 150(2) K, θ range = 3.04–25.00°. Final R [$I > 2\sigma(I)$]: $R1$ = 0.0319, $wR2$ = 0.0762; R (all data): $R1$ = 0.0435, $wR2$ = 0.0804.

CCDC-728134-728137 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): NMR, X-ray data tables, NMR spectra, and general methods.

Acknowledgments

The authors thank the Department of Science and Technology (DST), India, for financial assistance (Grant SR/S1/OC-19/2006), the Sophisticated Analytical Instruments Facility (SAIF), Indian Institute of Technology Bombay, for selected NMR spectroscopic data, and Dr. Mamta Dadwal for selected experimental data. I. D. and P. S. thank the Council of Scientific and Industrial Research (CSIR) for a senior research fellowship.

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[21] This also supersedes our original assignment of the *E* configuration for trifluoropyruvate adducts of aromatic and heteroaromatic nitroalkenes; see ref.[12]

[22] An intramolecular proton transfer of the type shown in Scheme 2, path A has been widely accepted as a prelude to the elimination step ever since it was first proposed by Hill and Isaacs [J. S. Hill, N. S. Isaacs, *J. Chem. Res. (S)* **1988**, 330]. There are several modifications to this in the recent literature (see ref.[4]), including that of McQuade (ref.[4g]) who proposed a hemiacetal intermediate in which case the TS will be a more acceptable six-membered ring.

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Received: May 4, 2009
Published Online: July 14, 2009

