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Nájera oxime-derived palladacycles catalyze intermolecular Heck reaction with Morita–Baylis–Hillman adducts. An improved and highly efficient synthesis of α-benzyl-β-ketoesters

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The authors dedicate this paper in memorium of the recently deceased Prof. Octávio Antunes for his outstanding contributions to brazilian palladium chemistry

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ABSTRACT

An improved and highly efficient synthesis of several α-benzyl-β-ketoesters from Morita–Baylis–Hillman adducts is described. These adducts were used as substrates for an intermolecular Heck reaction catalyzed by a Nájera oxime-derived palladacycles. These efficient catalytic conditions probed to be very selective providing only the corresponding functionalized β-ketoesters in high yield with no decarboxylation product. It seems that the method herein described is one of the most efficient for the synthesis of α-benzyl-β-ketoesters.

1. Introduction

The C–C σ bond is the backbone of organic molecules. Hence, the formation of new C–C bonds is one of the most important transformations in life. In organic chemistry, countless efforts have therefore been made to develop new, clean, and easy-to-handle methods to form such unique and crucial bonds.[1] Among the most efficient methods currently available, coupling reactions mediated by a transition-metal catalyst have been the most attractive. Their popularity resides in their mild conditions and applications to a great diversity of functional groups, usually unprotected.

The Heck reaction plays a important role among C–C bond formation methods catalyzed by transition metals.[2] Its high synthetic usefulness has stimulated a search for improved catalysts and experimental conditions. At present, Heck reactions can be performed efficiently using an infinitesimal amount of catalyst in the presence of moisture at room or moderate temperatures.

Palladacycles have recently attracted great attention as efficient Heck catalysts,[3] eliminating the need of phosphine addition. Examples of palladacycles used as Heck catalysts are the oxime-derived palladacycles developed by Nájera (Fig. 1).[4]

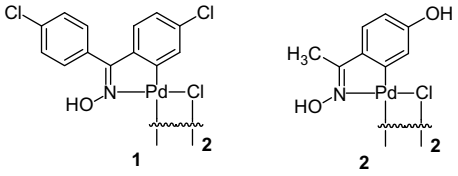

Figure 1. Oxime-derived palladacycles developed by Nájera.

The palladacycles **1** and **2** are thermally robust, and insensitive to both oxygen and moisture. They have been shown to function as efficient phosphine-free Heck precatalysts. In most cases, these palladacycles are a kind of palladium(0)-repository. Apparently, they form a nanoparticulate palladium under the reaction conditions, thus increasing their efficiency.[5]

Acrylates are interesting substrates for the preparation of a variety of functionalized cinnamates or 1,3-dicarbonyl compounds via Heck reaction (Scheme 1).[6,7]

An efficient method to produce such acrylates is the Morita–Baylis–Hillman (MBH) reaction.[8] Highly functionalized acrylates obtained via MBH reactions have already been used as substrates for Heck reactions.[9] However, MBH adducts are allylic alcohols, a structural moiety that usually forms a mixture of products when used as substrate for a Heck reaction, compromising both yield and

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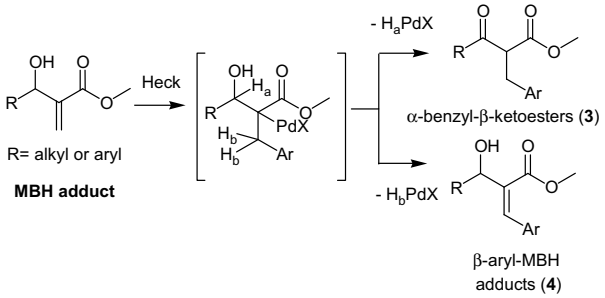


Scheme 1. Heck reaction using MBH adducts.

selectivity.[10a–c] Thus, this reaction normally produces the coupling products in moderate yields, resulting in the need for critical experimental protocols (high temperatures, long reaction times, special solvents).

The only exception was described some years ago by Basavaiah and Muthukumaran, in which the combination of $Pd(OAc)_2$/$NaHCO_3$/n-Bu_4NBr ('Jeffery protocol') was employed.[9a,10d–f] Despite the good yields, there is a long time of reflux, a high amount of palladium is used, and a small methodological scope, only having tested three different aryl bromides. Some years ago, we tried to use $Pd(OAc)_2$, alone or associated, to perform a Heck reaction with MBH adducts. These experimental conditions work nicely with some model acrylates, however failed when MBH adducts were used as substrates.[11]

An experimental protocol to prepare α-substituted cinnamates such as **4** (Scheme 1), in moderate to good yields, has been recently described by Kim et al.[9h] Some years ago, we described the synthesis of **3** using MBH adducts as substrates of a Heck reaction with diazonium salts in moderate yields (Scheme 1).[9f]

α-Benzyl-β-ketoesters such as **3** (Scheme 1) are important substrates for synthetic transformations, such as asymmetric dynamic resolution, asymmetric biotransformations, and the synthesis of heterocyclic compounds and natural products.[12]

The preparation of this type of compound requires the use of a special base, anhydrous conditions and low temperatures. Then, the use of a Heck reaction should be a very attractive alternative for their syntheses.

In a research program directed toward the asymmetric resolution of β-ketoesters, we needed to selectively prepare a set of α-benzyl-β-ketoesters. We therefore decided to search for conditions yielding optimal intermolecular Heck reactions using MBH adducts.

Herein we report a protocol leading to a simple, direct, selective, and fast synthesis of **3** and derivatives. It is based on an intermolecular Heck reaction of MBH adducts with aryl halides mediated by Nájera oxime-derived palladacycles. These palladacycles could contribute toward increasing the efficiency of an intermolecular Heck reaction with a particularly troublesome substrates such as Morita–Baylis–Hillman adducts.

2. Results and discussion

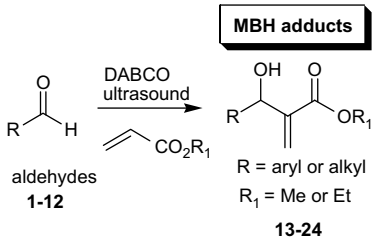
We start our investigation by preparing a set of different MBH adducts using a method previously described by our research group.[13]

Thus, aldehydes (**1**–**12**) were treated with an excess of methyl or ethyl acrylate in the presence of DABCO. The mixture was placed in an ultrasound bath to give the corresponding adducts in good to excellent yields (Table 1).

Having the adducts on hand, we began to evaluate the Nájera catalysts. Initially, we choose to work with catalyst **1** (Fig. 1), since it is the most adequate for reactions performed in organic solvents.

The intermolecular Heck reaction between the adduct obtained from benzaldehyde and phenyl iodide was used as a model to test for reaction feasibility as well as determine the best catalyst

Table 1
Preparation of Morita–Baylis–Hillman adducts



Entry	MBH adducts	(%)[a]
1	**13**, R=Phenyl; R_1=OCH_3	91
2	**14**, R=Phenyl; R_1=OEt	71
3	**15**, R=4-OMe-Ph; R_1=OEt	81
4	**16**, R=4-^{t}Butyl-Ph; R_1=OEt	76
5	**17**, 4-NO_2-Ph; R_1=OEt	96
6	**18**, R=4-ClPh; R_1=OEt	90
7	**19**, R=Piperonyl; R_1=OEt	65
8	**20**, R=Piperonyl; R_1=OCH_3	70
9	**21**, R=3,5-di-Fluoro-Phenyl; R_1=OMe	91
10	**22**, R=3,5-di-Fluoro-Phenyl; R_1=OEt	94
11	**23**, R=3-Pyridinyl; R_1=OCH_3	80
12	**24**, R=CH_2CH_3; R_1=OEt	85

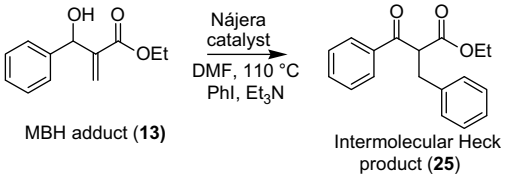
[a] Yields refer to isolated and purified products (by silica gel column chromatography).

concentration. Based on the results previously disclosed by Nájera,[4] a concentration of 0.001 mol % of **1** was employed initially. However, no coupling product was observed after several hours.

The second experiment (now using 0.01 mol % of catalyst) was monitored each 15 min, however we observed no significant conversion after 3 h time. After that, all experiments were performed for 15 h and monitored by C.G. chromatography. Every three hours, an aliquot was collected, treated, and analysed by HP-5 column chromatography. To our delight we were able to observe only a modest conversion of 22% after 3 h, which increased to 64% after 7 h. No higher conversion percentage was observed ever after 15 h. We next investigated the impact of the catalyst concentration. The results of this study are summarized in Table 2.

The increase in the catalyst concentration led to a direct increase in conversion resulting in a shortened net reaction time (compare entries 2, 5 and 6). The best experimental conditions were in which

Table 2
Evaluation of the concentration of Nájera catalyst (**1**) for the intermolecular Heck reaction with MBH adducts



Entry	Reaction conditions[a]	Conversion (%)[b,c]		
	Catalyst (mol %)	**3h**	**7h**	**15h**
1	0.001	0	0	0
2	0.01	22	64	—
3	0.025	32	62	—
4	0.05	46	60	—
5	0.1	54	62	90
6	0.25	92	—	—
7	0.5	>98	—	—
8	0.75	85	—	—
9	1.0	76	—	—

[a] All reactions were performed in DMF at 110 °C, using triethylamine as base.
[b] Conversions were determined by GC chromatography using a HP-5 column.
[c] No alteration was detected in conversion when a longer warming period was used (24 h).

0.5 mol % of catalyst **1** was employed (see entry 7), in a solution of DMF warmed at 110 °C, in the presence of triethylamine for 3 h. Under this simple and relatively easy protocol the intermolecular Heck products were obtained very clean with very good yields and selectivity, after purification by silica gel column chromatography. 1,3-Dicarbonyl compounds are prone to decarboxylate under warming, however when the methyl esters were used, only a tiny amount of decarboxylation product was detected. Replacing the methyl ester for the corresponding ethyl ester led to the desired Heck product with no decarboxylation product detected (Table 2). We also observed that shorter reaction times avoid decarboxylation side products, allowing the use of both methyl or ethyl esters equally.

The concentration of 0.5 mol % was then used as a standard concentration for the next steps. Different MBH adducts were submitted to coupling reactions with phenyl iodide, bromide and aryl iodides (Table 3).

Table 3
Heck reaction between MBH adducts and aryl halides catalyzed by Nájera palladacycle **1**

Entry	MBH adduct	Reaction conditions[a]		Yield[b,c] (%)
		ArX	Base	
1	**13**	PhI	Et_3N	**25**, 81
2	**13**	4-NO_2-PhI	Et_3N	**26**, 30
3	**14**	PhI	Et_3N	**27**, 85
4	**14**	PhBr	K_2CO_3[d]	**27**, 83
5	**15**	PhI	Et_3N	**28**, 95
6	**16**	PhI	Et_3N	**29**, 78
7	**17**	PhI	Et_3N	**30**, 85
8	**18**	PhI	Et_3N	**31**, 81
9	**19**	PhI	Et_3N	**32**, 85
10	**20**	4-MeO-PhI	Et_3N	**33**, 84
11	**20**	4-HO-PhI[e]	Et_3N	**34**, 87
12	**21**	PhI	Et_3N	**35**, 89
13	**22**	PhI	Et_3N	**36**, 79
14	**22**	PhBr	K_2CO_3[d]	**36**, 82
15	**23**	PhI	Et_3N	**37**, 70
16	**24**	PhI	Et_3N	**38**, 87

[a] Reactions were carried out in DMF at 110 °C for 3 h.
[b] Yields refer to isolated and purified products.
[c] In some cases, besides the Heck coupling product a tiny amount (2–4%) of starting material was detected, however without consequences for the yield.
[d] In this particular case TBAB should be used as additive and the reaction was performed at 130 °C.
[e] In this case was used 2.8 equiv of Et_3N.

In every case, the yields were higher than those described previously using diazonium salts.[9f] The reaction time and yields are also better than some described using $Pd(OAc)_2$.[8a–e,g,i]

The reaction works quite well with all MBH adducts tested, regardless of the nature of aromatic substituents. The only exception occurred when 4-nitro-iodophenol was used (entry 2, Table 3). In this particular case a low yield was observed, although no optimization has been performed Nevertheless, the reaction worked well even for heterocyclic aromatic rings (see entry 15). The reactions are very clean and can be easily purified by usual chromatographic methods. We also achieved a high degree of selectivity with no mixture of products detected. This result was remarkable considering that our substrates were highly functionalized allylic alcohols.

In summary, a very efficient strategy to synthesize highly functionalized β-ketoesters from MBH adducts has been established. The selectivity observed is high with no detected side products. Currently, it seems to be the most efficient phosphine-free Heck reaction using MBH adducts, and may be used to afford a myriad of useful intermediates for organic synthesis. This protocol is more efficient than the Jeffery protocol, since the amount of catalyst and the reaction time are lower.

Although those types of β-ketoesters could be prepared by direct benzylation of 1,3-dicarbonyl compounds, the strategy described herein is a valuable alternative for the preparation of these compounds. It does not require special experimental conditions (non-nucleophilic bases, special enolates, low temperature), and avoids mixtures of products normally obtained when different esters are used in a classical Claisen reaction.[14] This is also the first report describing the use of palladacycles to perform an intermolecular Heck reaction with MBH adducts. Further studies are ongoing in our laboratory aiming at extending the scope of this reaction. We intend to develop intramolecular versions that will be disclosed in due time.

3. Experimental

3.1. General methods

The following procedures are representative for all the Baylis-Hillman adducts and α-benzyl-β-ketoesters prepared in this work. All the reagents were purchased from specialized suppliers with analytical purity and were utilized without previous purification, unless noted. The ^1H and ^{13}C spectra were recorded on a Bruker at 250 MHz and 62.5 MHz, respectively, or on an Inova instrument at 500 MHz and 125 MHz, respectively. The mass spectra were recorded using a Micromass (Manchester, UK) QT of instrument of ESI-QT of configuration with 5000 mass resolution and 50 ppm mass accuracy in the TOF mass analyzer. IR were obtained with a Nicolet model Impact 410. Only the spectral data of the unknown Morita–Baylis–Hillman adducts are enclosed.

3.2. General experimental protocol for the preparation of the Morita–Baylis–Hillman adducts

A mixture of aldehyde (1–2 mmol, **1**–**12**), methyl or ethyl acrylate (20 equiv, used as reagent and solvent), and DABCO (0.65 equiv) was sonicated (180 W, 25 kHz) for a certain period of time (5–96 h). The ultrasound bath temperature was constantly monitored and kept at 30–40 °C during the reaction, through ice addition or by using a refrigerated circulator. After the reaction time, the mixture was evaporated under reduced pressure in order to remove the excess of acrylate. The residue was diluted with dichlorometane or ethyl acetate (30 mL). The organic solution was washed with 10% aqueous HCl (2×10 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4. After filtration and solvent removal, the residue was filtered through a pad of gel of silica to afford the corresponding Morita-Baylis-Hillman adducts (**13**–**24**) in good to excellent yield.

3.3. General experimental protocol for the synthesis of α-benzyl-β-keto esters

A 10-mL round-bottom flask was charged with 4-iodophenol (81.4 mg, 0.37 mmol), Morita–Baylis–Hillman adduct **8** (127 mg, 0.54 mmol), triethylamine (0.2 mL, 1.51 mmol), palladacycle **1** (2.2 mg, 0.0027 mmol, 0.5 mol % Pd) and DMF (2-3 mL). The mixture was stirred at 110 °C in air and the reaction progress was analyzed by TLC. The crude reaction mixture was extracted with water and EtOAc (3×15 mL). The organic phase was dried over Na_2SO_4, evaporated and the resulting crude product was purified by silica gel flash chromatography (hexane/EtOAc) to give the corresponding α-benzyl-β-keto ester.

3.4. General protocol for the Heck coupling with aryl bromide

A 10-mL, round-bottom flask was charged with aryl bromide (40μL, 0.38 mmol), Morita–Baylis–Hillman adducts **22** (77.3 mg, 0.32 mmol), potassium carbonate (62 mg, 0.45 mmol),

tetrabutylamonium bromide (21 mg, 0.064 mmol, 20 mol %), palladacycle **1** (1.3 mg, 0.0016 mmol, 0.5 mol % Pd) and DMF (2–3 mL). The mixture was stirred at 130 °C in air and the reaction progress was analyzed by TLC. The reaction mixture was diluted in ethyl acetate (30 mL) and washed with distilled water (4×10 mL). The organic phase was dried over Na_2SO_4 and evaporated. The crude residue was purified by preparative thin layer chromatography to give the corresponding α-benzyl-β-keto ester (**36**).

3.5. Characterization data

*3.5.1. Ethyl 2-[hydroxy(phenyl)methyl]prop-2-enoate (**14**)*

Pale yellow viscous oil. 71% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.24 (m, 5H); 6.34 (t, *J*=1.0 Hz, 1H); 5.81 (t, *J*=1.2 Hz, 1H); 5.56 (d, *J*=3.5 Hz, 1H); 4.18 (q, *J*=7.1 Hz, 2H); 3.08 (d, *J*=5.0 Hz, 1H); 1.24 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 167.7; 140.8; 140.4; 128.9; 128.2; 128.0; 127.0; 75.3; 60.5; 14.0. IR (film, λ_{max}): 3451, 1715, 1628, 1493, 1453, 1370, 1271, 1175, 1149, 1079, 765 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{12}H_{14}O_3$ 206.2378. Found: 229.0891 [M$^+$•+Na (23)].

*3.5.2. Ethyl 2-[hydroxy(4-methoxyphenyl)methyl]prop-2-enoate (**15**)*

Viscous yellow oil. 81% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27 (d, *J*=8.5 Hz, 2H); 6.86 (d, *J*=8.8 Hz, 2H); 6.30 (t, *J*=1.1 Hz, 1H); 5.84 (t, *J*=1.3 Hz, 1H); 5.50 (sl, 1H); 4.15 (q, *J*=7.1 Hz, 2H); 3.78 (s, 3H); 3.12 (sl, 1H); 1.23 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3; 159.0; 142.3; 133.5; 127.8; 125.2; 113.6; 72.6; 60.8; 55.1; 13.9; IR (film, λ_{max}): 3465, 1714, 1611, 1512, 1465, 1396, 1370, 1251, 1034 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{13}H_{16}O_4$ 236.1049. Found: 259.0948 [M$^+$•+Na (23)].

*3.5.3. Ethyl 2-[(4-tert-butylphenyl)(hydroxy)methyl]prop-2-enoate (**16**)*

Viscous yellow oil. 76% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (dd, *J*=8.5 Hz and *J*=18.6 Hz, 4H); 6.32 (s, 1H); 5.87 (s, 1H); 5.53 (d, *J*=4.9 Hz, 1H); 4.14 (q, *J*=7.3 Hz, 2H); 3.37 (d, *J*=5.3 Hz, 1H); 1.32 (s, 9H); 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3; 150.5; 142.5; 138.5; 126.4; 125.3; 125.2; 72.7; 60.8; 34.5; 31.4; 14.0; IR (film, λ_{max}): 3449, 2964, 1717, 1629, 1510, 1456, 1407, 1270, 1149, 1041 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{16}H_{22}O_3$ 262.1569. Found: 285.1483 [M$^+$•+Na (23)].

*3.5.4. Ethyl 2-[hydroxy(4-nitrophenyl)methyl]prop-2-enoate (**17**)*

Orange oil. 96% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.20 (d, *J*=8.9 Hz, 2H); 7.60 (d, *J*=8.5 Hz, 2H); 6.39 (s, 1H); 5.86 (s, 1H); 5.62 (s, 1H); 4.18 (q, *J*=7.1 Hz, 2H); 3.43 (sl, 1H); 1.26 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 165.9; 148.7; 147.3; 141.1; 127.3; 127.0; 123.5; 72.7; 61.3; 14.0; IR (film, λ_{max}): 3483, 1711, 1629, 1607, 1522, 1401, 1349, 1269, 1176, 1109 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{12}H_{13}NO_5$ 251.0794. Found: 274.0739 [M$^+$•+Na (23)].

*3.5.5. Ethyl 2-[1,3-benzodioxol-5-yl(hydroxy)methyl]prop-2-enoate (**19**)*

Pale yellow oil. 65% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.81–6.70 (m, 3H); 6.29 (s, 1H); 5.89 (s, 2H); 5.84 (s, 1H); 5.42 (s, 1H); 4.13 (q, *J*=7.1 Hz, 2H); 3.36 (s, 1H); 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.2; 147.6; 147.1; 142.3; 135.5; 125.2; 120.3; 108.0; 107.2; 101.0; 72.6; 60.9; 14.0; IR (film, λ_{max}): 3449, 2983, 1714, 1629, 1503, 1488, 1443, 1249, 1039 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{13}H_{14}O_5$ 250.0841. Found: 273.0776 [M$^+$•+Na (23)].

*3.5.6. Methyl 2-[(3,5-difluorophenyl)(hydroxy)methyl]prop-2-enoate (**21**)*

Colorless viscous oil. 91% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.96–6.87 (m, 2H); 6.72 (tt, *J*=2.4 Hz and *J*=8.9 Hz, 1H); 6.38 (s, 1H); 5.86 (t, *J*=1.0 Hz, 1H); 3.75 (s, 3H); 2.70 (sl, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.2; 164.9 (d, *J*=12.6 Hz, C–F aromatic); 161.0 (d, *J*=12.6 Hz, C–F aromatic); 145.5 (t, *J*=8.5 Hz); 140.9; 109.4 (d, *J*=25.5 Hz); 109.3 (d, *J*=7.8 Hz); 103.2 (t, *J*=25.4 Hz); 72.5 (t, *J*=2.1 Hz); 52.1; 46.3; IR (film): 3396, 1719, 1625, 1598, 1459, 1441, 1313, 1270, 1196, 1154, 1057, 991 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{11}H_{10}F_2O_3$ 228.0598. Found: 251.0408 [M$^+$•+Na (23)].

*3.5.7. Ethyl 2-[(3,5-difluorophenyl)(hydroxy)methyl]prop-2-enoate (**22**)*

Colorless viscous oil. 94% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.91 (dd, *J*=1.8 Hz and *J*=8.3 Hz, 2H); 6.69 (tt, *J*=2.3 Hz and 8.9 Hz, 1H); 6.35 (s, 1H); 5.87 (t, *J*=1.0 Hz, 1H); 5.47 (d, *J*=5.6 Hz, 1H); 4.15 (q, *J*=7.1 Hz, 2H); 3.97 (d, *J*=5.8 Hz, 1H); 2.47 (sl, 1H); 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.3; 164.9 (d, *J*=12.7 Hz, C–F aromatic); 160.9 (*J*=12.5 Hz, C–F aromatic); 146.2 (t, *J*=8.6 Hz); 141.7; 126.3; 109.4 (d, *J*=25.3 Hz); 109.3 (d, 8.1 Hz); 102.9 (t, *J*=25.3 Hz); 71.7 (t, *J*=2.3 Hz); 52.0; 46.5; IR (film, λ_{max}): 3453, 1710, 1625, 1598, 1462, 1372, 1312, 1119, 855 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{12}H_{12}F_2O_3$ 242.0755. Found: 265.2178 [M$^+$•+Na (23)].

*3.5.8. Ethyl 3-hydroxy-2-methylidenepentanoate (**24**)*

Colorless viscous oil. 85% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.23 (d, *J*=1.0 Hz, 1H); 5.77 (t, *J*=1.2 Hz, 1H); 4.32 (t, *J*=6.6 Hz, 1H); 4.23 (q, *J*=7.1 Hz, 2H); 2.65 (sl, 1H); 1.76–1.62 (m, 2H); 1.32 (t, *J*=7.1 Hz, 3H); 0.95 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.6; 142.2; 124.9; 73.2; 60.8; 29.0; 14.1; 10.1; IR (film): 3447, 2976, 1714, 1629, 1464, 1373, 1274, 1176, 1159 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_8H_{14}O_3$ 158.0943. Found: 181.0912 [M$^+$•+Na (23)].

*3.5.9. Methyl 2-benzyl-3-oxo-3-phenylpropanoate (**25**)*

Yellow viscous oil. 81% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.99–7.93 (m, 2H); 7.59–7.40 (m, 3H); 7.25–7.17 (m, 5H); 4.66 (t, *J*=7.4 Hz); 3.68 (s, 3H); 3.33 (dd, *J*=2.4 Hz and 7.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 194.4; 169.6; 138.2; 136.0; 135.5; 128.8; 128.7; 128.6; 128.5; 126.6; 55.8; 52.5; 34.8; IR (film, λ_{max}): 3463, 1741, 1686, 1596, 1581, 1448, 1435 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{17}H_{16}O_3$ 268.1099. Found: 291.0997 [M$^+$•+Na (23)].

*3.5.10. Methyl 2-(4-nitrobenzyl)-3-oxo-3-phenylpropanoate (**26**)*

Pale yellow viscous oil. 30% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.37 (d, *J*=8.9 Hz, 1H); 8.01–7.96 (m, 2H); 7.79 (d, *J*=8.9 Hz, 1H); 7.60 (tt, *J*=1.3 Hz and *J*=7.2 Hz, 1H); 7.52–7.45 (m, 2H); 7.26 (s, 1H); 4.42 (q, *J*=7.1 Hz, 1H); 3.69 (s, 3H); 1.51 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 195.8; 171.3; 135.7; 133.5; 128.8; 128.6; 128.3; 124.4; 53.4; 52.5; 48.0; 29.7; 13.8; IR (film, λ_{max}): 3444, 1736, 1678, 1605, 1528, 1496, 1455, 1347, 1269 cm^{-1}. HRMS (EI$^+$, *m*/*z*) Calcd for $C_{17}H_{15}NO_5$ 313.0950. Found: 314.0983 [M$^+$•+H].

*3.5.11. Ethyl 2-benzyl-3-oxo-3-phenylpropanoate (**27**)*

Pale yellow viscous oil. 83% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.00–7.94 (m, 2H); 7.60–7.42 (m, 3H); 7.24–7.21 (m, 5H); 4.62 (t, *J*=7.3 Hz, 1H); 4.19–4.04 (m, 2H); 3.33 (d, *J*=7.2 Hz, 2H); 1.11 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ IR (film, λ_{max}): 3369, 2959, 1734, 1687, 1598, 1582, 1496, 1449, 1368, 1270, 1231, 1152, 749 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{18}H_{18}O_3$ 282.1256. Found: 305.1079 [M$^+$•+Na (23)].

*3.5.12. Ethyl 2-benzyl-3-(4-methoxyphenyl)-3-oxopropanoate (**28**)*

Yellow viscous oil. 95% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.93–7.94 (m, 2H); 7.26–7.17 (m, 4H); 6.96–6.88 (m, 2H); 4.61–4.29 (m, 1H); 4.19–4.03 (m, 2H); 3.85 (s, 3H); 3.31 (dd, *J*=3.5 Hz and 7.6 Hz); 1.12 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.7; 169.4; 163.8; 138.5; 131.0; 128.9; 128.4; 126.5; 113.8; 61.3; 61.2; 55.8; 55.4; 34.7; 13.8; IR (film, λ_{max}): 3341, 1736, 1677, 1601, 1575, 1511, 1496, 1450, 1308, 1173 cm^{-1}. HRMS (ESI, *m*/*z*) Calcd for $C_{19}H_{20}O_4$ 312.1362. Found: 335.1226 [M$^+$•+Na (23)].

*3.5.13. Ethyl 2-benzyl-3-(4-tert-butylphenyl)-3-oxo-propanoate (**29**)*

Yellow viscous oil. 78% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.93–7.90 (m, 2H); 7.50–7.44 (m, 2H); 7.29–7.20 (m, 5H); 4.61 (t, J=7.4 Hz, 1H); 4.20–4.01 (m, 2H); 3.31 (dd, J=2.3 Hz and 7.6 Hz); 1.32 (s, 9H); 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.9; 169.4; 157.4; 138.6; 133.5; 128.9; 128.6; 128.5; 126.5; 125.7; 61.4; 56.1; 34.7; 31.0; 13.9; IR (film, λ_{max}): 3358, 2965, 1737, 1684, 1605, 1565, 1496, 1450, 1270, 1194 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{22}H_{26}O_3$ 338.1882. Found: 339.1851 [M$^+$•+H].

*3.5.14. Ethyl 2-benzyl-3-(4-nitrophenyl)-3-oxopropanoate (**30**)*

Orange viscous oil. 85% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.27 (d, J=9.0 Hz, 2H); 8.06 (d, J=9.0 Hz, 2H); 7.29–7.18 (m, 5H); 4.62 (t, J=7.4 Hz, 1H); 4.12 (q, J=6.8 Hz, 2H); 3.35 (d, J=7.4 Hz, 2H); 1.13 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.4; 168.5; 150.4; 140.7; 137.7; 129.5; 128.8; 128.6; 126.8; 123.8; 61.9; 56.6; 34.6; 13.9; IR (film, λ_{max}): 3445, 1737, 1650, 1605, 1528, 1496, 1455, 1347, 1269 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{18}H_{17}NO_5$ 327.1107. Found: 350.1030 [M$^+$•+Na (23)].

*3.5.15. Ethyl 2-benzyl-3-(4-chlorophenyl)-3-oxopropanoate (**31**)*

Colorless viscous oil. 81% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.88 (d, J=8.4 Hz, 2H); 7.41 (d, J=8.0 Hz, 2H); 7.23 (s, 5H); 4.56 (t, J=7.3 Hz, 1H); 4.10 (q, J=7.1 Hz, 2H); 3.32 (d, J=7.3 Hz, 2H); 1.12 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.3; 169.0; 140.0; 138.1; 134.5; 130.0; 129.0; 128.8; 128.5; 61.6; 56.1; 48.3; 34.6; 13.9; IR (film, λ_{max}): 3402, 1737, 1687, 1589, 1571, 1455, 1401, 1368, 1231, 1093 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{18}H_{17}ClO_3$ 316.0866. Found: 339.0726 [M$^+$•+Na (23)].

*3.5.16. Ethyl 3-(1,3-benzodioxol-5-yl)-2-benzyl-3-oxo-propanoate (**32**)*

Pale yellow viscous oil. 85% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.57 (dq, J=1.8 Hz and 4.5 Hz, 1H); 7.45 (dd, J=1.8 Hz and 5.0 Hz, 1H); 6.84 (dd, J=8.2 Hz and 10.1 Hz); 6.04 (d, J=4.2 Hz, 2H); 4.53 (t, J=7.4 Hz); 4.19–4.04 (m, 2H); 3.30 (dd, 1.7 Hz and 7.5 Hz, 1H); 1.47 (d, J=7.1 Hz, 1H); 1.16 (dt, J=7.1 Hz and 14.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.3; 169.3; 152.1; 148.3; 138.4; 130.9; 128.8; 128.4; 126.5; 125.1; 108.3; 107.8; 101.9; 61.4; 55.8; 48.0; 34.8; 13.9; IR (film, λ_{max}): 3439, 1735, 1677, 1604, 1505, 1489, 1442, 1354, 1261, 1038 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{19}H_{18}O_5$ 326.1154. Found: 349.1059 [M$^+$•+Na (23)].

*3.5.17. Methyl 3-(1,3-benzodioxol-5-yl)-2-(4-methoxybenzyl)-3-oxopropanoate (**33**)*

Pale yellow oil; 84% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55 (dd, J=1.8 Hz and 6.5 Hz, 1H); 7.43 (d, J=1.7 Hz, 1H); 7.12 (d, J=8.8 Hz, 2H); 6.84–6.77 (m, 3H); 6.03 (s, 2H); 4.51 (t, J=7.3 Hz, 1H); 3.80 (s, 3H); 3.64 (s, 3H); 3.25 (dd, J=1.9 Hz and Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.4; 169.8; 158.3; 152.2; 148.3; 131.0; 130.3; 129.8; 125.2; 113.9; 108.3; 107.9; 101.9; 55.9; 55.1; 52.5; 34.1; IR (film, λ_{max}): 3518, 2954, 1740, 1677, 1611, 1513, 1489, 1443, 1250, 1159, 1037 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{19}H_{18}O_6$ 342.1103. Found: 365.0737 [M$^+$•+Na (23)].

*3.5.18. Methyl 3-(1,3-benzodioxol-5-yl)-2-(4-hydroxybenzyl)-3-oxopropanoate (**34**)*

Pale yellow viscous oil. 87% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55 (dd, J=1.7 Hz and 8.3 Hz, 1H), 7.42 (d, J=1.7 Hz, 1H), 7.06 (d, J=8.5 Hz, 2H), 6.82 (d, J=8.2 Hz, 1H), 6.70 (d, J=8.5 Hz, 2H), 6.04 (s, 2H), 4.51 (t, J=7.4 Hz, 1H), 3.64 (s, 3H), 3.23 (dd, J=7.4 Hz and 2.1 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.1, 170.3, 154.7, 152.5, 148.4, 130.8, 130.0, 129.8, 125.4, 115.5, 108.3, 108.0, 102.1, 56.0, 52.7, 34.3; IR (film, λ_{max}): 3417, 1736, 1673, 1613, 1604, 1516, 1505, 1489, 1444, 1357, 1255, 1038 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{18}H_{16}O_6$ 328.0947. Found: 351.0697 [M$^+$•+Na (23)].

*3.5.19. Methyl 2-benzyl-3-(3,5-difluorophenyl)-3-oxo-propanoate (**35**)*

Pale yellow viscous oil. 89% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47–7.38 (m, 2H); 7.26–7.18 (m, 5H); 7.04–6.96 (m, 1H); 4.52 (t, J=7.4 Hz, 1H); 3.67 (s, 3H); 3.33 (d, J=7.4 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.2; 169.0; 165.0 (d, J=11.8 Hz, C–F aromatic); 161.0; (d, J=11.8 Hz, C–F aromatic); 139.0 (t, J=7.6 Hz); 137.7; 128.7 (d, J=11 Hz); 126.9; 111.6 (d, J=26.1 Hz); 111.6 (d, J=7.5 Hz); 111.5 (d, J=26.1 Hz); 108.9 (t, J=25.4 Hz); 56.1; 52.8; 34.7; IR (film, λ_{max}): 3366, 1744, 1697, 1618, 1596, 1497, 1455, 1440, 1320, 1124, 988 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{17}H_{14}F_2O_3$ 304.0911. Found: 305.0836 [M$^+$•+H].

*3.5.20. Ethyl 2-benzyl-3-(3,5-difluorophenyl)-3-oxo-propanoate (**36**)*

Pale yellow viscous oil. 82% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.42 (m, 2H); 7.26–7.19 (m, 5H); 7.05–6.96 (m, 1H); 4.49 (t, J=7.4 Hz, 1H); 4.13 (dq, 2H); 3.32 (d, J=7.4 Hz, 2H); 1.14 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.2; 168.6; 164.9 (d, J=11.7 Hz, C–F aromatic); 160.9 (d, J=11.8 Hz, C–F aromatic); 139.1 (t, J=7.6 Hz); 137.8; 128.9; 128.6; 126.8; 111.5 (d, J=26.0 Hz); 111.4 (d, J=7.3 Hz); 108.8 (t, J=25.4 Hz); 61.8; 56.4; 34.6; 13.9; IR (film, λ_{max}): 3378, 1739, 1698, 1619, 1596, 1497, 1455, 1440, 1322, 1264, 1210, 1145, 1124, 988 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{17}H_{14}F_2O_3$ 304.0911. Found: 305.0836 [M$^+$•+H].

*3.5.21. Methyl 2-benzyl-3-oxo-3-(pyridin-3-yl)propanoate (**37**)*

Yellow viscous oil. 70% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.19–9.12 (m, 1H); 8.81–8.74 (m, 1H); 8.28–8.16 (m, 1H); 7.47–7.17 (m, 6H); 4.64 (t, J=7.4 Hz, 1H); 3.66 (s, 3H); 3.35 (d, J=7.8 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 193.6; 169.1; 153.7; 149.9; 137.7; 135.9; 128.8; 128.6; 126.8; 123.6; 56.0; 52.7; 34.5; IR (film, λ_{max}): 3463, 1739, 1686, 1594, 1580, 1446, 1433 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{16}H_{15}NO_3$ 269.1052. Found: 270.0978 [M$^+$•+H].

*3.5.22. Ethyl 2-benzyl-3-oxopentanoate (**38**)*

Tinged yellow viscous oil. 87% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30–7.15 (m, 5H); 4.13 (q, J=7.1 Hz, 2H); 3.79 (t, J=7.6 Hz, 1H); 3.16 (d, J=7.7 Hz, 2H); 2.45 (dq, J=7.2 Hz and 35.6 Hz); 1.20 (t, J=7.1 Hz, 3H); 1.00 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 192.3; 169.3; 152.1; 152; 148.3; 148.2; 138.4; 130.9; 128.8; 128.4; 126.5; 125.1; 108.3; 107.8; 101.9; 61.4; 55.8; 48; 34.8; 13.9; IR (film, λ_{max}): 3425, 3027, 1742, 1716, 1497, 1455, 1368, 1268, 1204, 750 cm^{-1}. HRMS (ESI, m/z) Calcd for $C_{14}H_{18}O_3$ 234.1256. Found: 257.1057 [M$^+$•+Na (23)].

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Supplementary data

Spectra of some unknown MBH adducts and of all α-benzyl-β-ketoesters are supplied as supplementary material. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.084.

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