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A Facile, Versatile, and Mild Morita–Baylis–Hillman-Type Reaction for the Modular One-Pot Synthesis of Highly Functionalized MBH Adducts

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Keywords: Multicomponent reactions / Domino reactions / Michael addition / Aldol reactions / Selenium

Morita–Baylis–Hillman derivatives have been extensively investigated as intermediates in the preparation of important classes of compounds. However, there are intrinsic limitations regarding the structure of the Michael electrophile acceptors, the aldehydes, and the catalysts. Therefore, this transformation has several drawbacks, including, for example, its long reaction times. Herein we present a simple, general, fast, and high-yielding protocol for the one-pot synthesis of Morita–Baylis–Hillman derivatives. Our approach is driven by a lithium selenolate Michael/aldol operation with concomitant *O*-functionalization/selenoxide elimination cascade sequences.

Introduction

Among all C–C bond-formation reactions, the aldol and Michael reactions have always been among the most important methodologies. Moreover, Michael/aldol tandem reactions, in addition to promoting multiple C–C bond formations, also lead to important carbon skeletons that can be strategically employed as building blocks for the synthesis of a large number of natural products.[1] Metal organochalcogenolates are an important class of nucleophiles in Michael/aldol tandem reactions due to their excellent Pearson's soft nucleophilicity and extremely low Brønsted basicity. Furthermore, the easy removal of the chalcogen moiety by oxidative elimination leading to Morita–Baylis–Hillman (MBH) adducts makes these entities appealing for this transformation. The possibility of generating these nucleophiles in situ from commercially available elemental chalcogen is also an attractive alternative, as no malodorous chemicals/starting materials need to be handled and the final chalcogen oxidized derivative byproduct is innocuous and odorless.[2] In the last years, MBH derivatives, especially carbonates[3,4] and acetates,[5–15] have been described as important intermediates in the synthesis of different frameworks, and these compounds have become important as MBH precursors, It has been reported that they also represent a valuable class of substrates for synthetic purposes.[16–19] In this work, we report our results on the first general, high-yielding, and fast tandem reaction protocol for the synthesis of different MBH derivatives by using lithium selenolates as the initial nucleophile.

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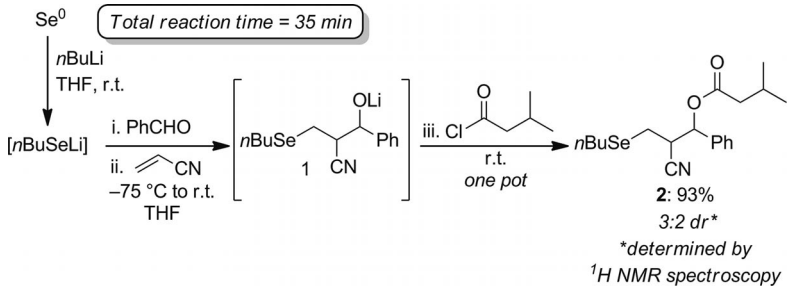
Results and Discussion

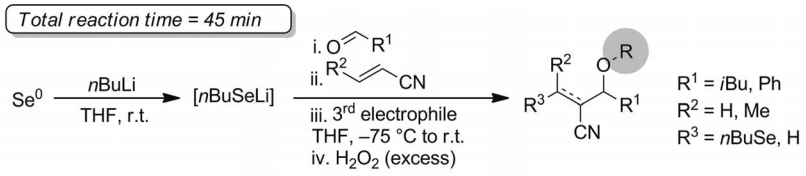
It has been previously demonstrated that lithium *n*-butylselenolate undergoes selective 1,4-addition to acrylonitrile as well as acrylic esters in the presence of aldehydes to yield the corresponding Michael/aldol products. In comparison to lithium phenylselenolate, usually employed in Michael[20] and homo-Michael[21] type reactions, *n*-alkylselenolates are more reactive and easier to prepare. More specifically, the preparation of *n*-butylselenolate makes use of a common organolithium reagent (*n*BuLi) and completely avoids the formation of volatile selenides and diselenides, like that observed when employing MeLi. In an attempt to extend the methodology and study its scopes and limitations, we envisioned that the Michael/aldol, alkoxide functionalization, and *n*-butylselenium moiety elimination sequence could be possible in a one-pot operation, leading to *O*-functionalized MBH derivatives. As a proof-of-principle experiment, we submitted benzaldehyde and acrylonitrile to a reaction with lithium *n*-butylselenolate, followed by quenching the reaction media with isovaleroyl chloride aiming to isolate the corresponding ester. Expected product **2** was obtained in high yield and low diastereoselectivity, as depicted in Scheme 1.

As previously described in the literature, there are many oxidants capable of promoting the oxidation of organic selenides to selenoxides.[22] However, hydrogen peroxide presents some advantages over other oxidants due to the fact that its oxidation reaction is much faster than those using any other oxidants.[16] In addition, hydrogen peroxide has been shown to be compatible under similar reaction conditions,[2] and its use minimizes selenylated byproducts. Moreover, it is one of the greenest chemicals, as its byproduct is water. We have found that 6 equiv. of this oxidant led to the total conversion of the selenylated intermediate into the MBH adduct in high yields. In these experiments we evaluated the behavior of different aldehydes and Michael ac-



Scheme 1. One-pot Michael/aldol/*O*-functionalization selenolate-mediated reaction.

Table 1. Initial screening of aldehydes and the thrid electrophile followed by selenium oxidative elimination.



Entry	3rd electrophile	Product/Yield	Entry	3rd electrophile	Products/Yield
1	1.0 equiv.	**3** 90%	5	1.0 equiv.	3:2 *dr** **7** 94%
2	1.0 equiv.	**4** 82%	6	1.0 equiv.	**8** 89%
3	1.0 equiv.	**5** 93%	7	1.0 equiv.	**9** 87%
4	1.0 equiv.	**6** 91%	8	1.0 equiv.	**10** 84%

ceptors as well as acid chlorides and other *O*-functionalizing electrophiles, like triisopropylsilyl chloride, Cbz, and Boc_2O (the last two, carbonate precursors). When TIPSCl was employed as the third electrophile, the selenoxide elimination step was not performed due to the sensitivity of these groups under oxidative conditions. To test this concept, we started the cascade reactions by employing acrylonitrile and benzaldehyde as Michael/aldol partners, varying the third electrophile, followed by oxidative selenium elimination. The results of these experiments are summarized in Table 1.

As shown above, in our initial study we have produced some different *O*-functionalized MBH adducts by employing classical substrates like benzaldehyde and acrylonitrile and some different acid chloride (Table 1, Entries 1–4) in very good yields. Besides acid chlorides, the intermediate alkoxides were also appropriately functionalized to produce a benzyl carbonate (Table 1, Entry 2). It is worth noting that even when employing a β-substituted Michael acceptor (Table 1, Entry 5) the expected product was obtained in a very high yield with 3:2 *dr*, the same ratio as that obtained for compound **2**, which was not submitted to selenoxide elimination.

The same good results were also observed when employing nonactivated alkyl aldehydes in combination with different acid chlorides, leading to the expected *O*-functionalized MBH products in good yields and in the same reaction time (Table 1, Entries 6–8). As it can be observed, in contrast to the classic MBH reaction, this methodology shows no limitation when employing nonactivated aldehydes, even at low temperatures, yielding the expected products in very short reaction times (45 min).

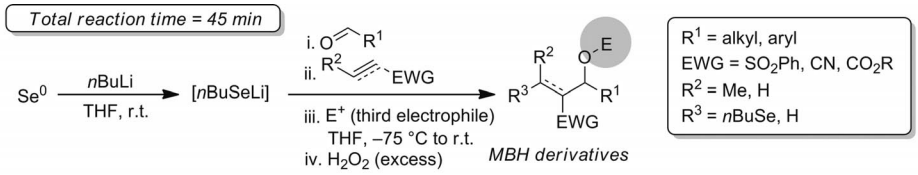
As the structural diversity of these derivatives must be widely scalable, the use of different aldehydes as well as different Michael acceptors and the third electrophiles is very important to carry different chemical functions to further transformations. In this context, a wider range of examples was produced looking forward to extend the methodology.

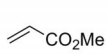
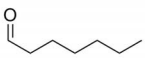
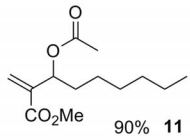
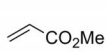
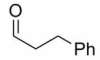
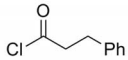
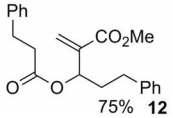
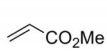
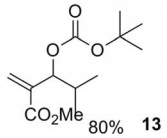
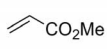
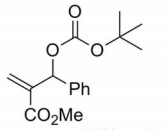
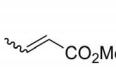
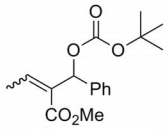
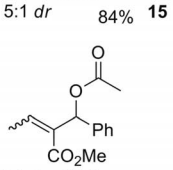
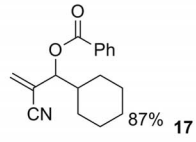
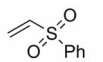
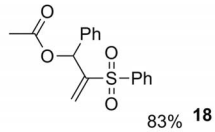
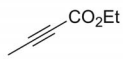
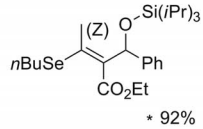
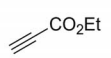
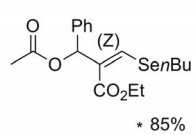
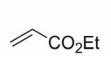
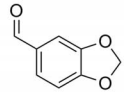
Amongst the results displayed in Table 2 it is also worth noting that β-methyl-substituted acetylenic esters as Michael acceptors (Table 2, Entry 9) leads to the expected products in good yields, showing that the steric hindrance or electronic effects from the methyl group (Table 1, Entry 5; Table 2, Entries 5 and 6) is not significant when employing selenolate nucleophiles.

When the Michael acceptors were acetylenic esters, the geometry of the resulting double bond was determined by NOE experiments to be exclusively *Z* in both cases (Table 2, Entries 9 and 10), and these results are in agreement with previous results concerning the β-chalcogeno-functionalization of acetylenic Michael acceptors.[23–25] The same NOE enhancement pattern shown in Figure 1 for compound **20** was also observed for compound **19**.

Willing to justify the complementarity of the present methodology to the MBH reaction, it is important to investigate the drawbacks of the MBH reaction. We have already shown that β-methyl-substituted Michael acceptors are very reactive towards this protocol, but one of the most serious drawbacks of the classic MBH reaction is the use of electron-rich aldehydes. Therefore, we decided to test piperonal and 3,4,5-trimethoxybenzaldehyde, two very electron-rich aromatic aldehydes and, fortunately, both of the aldehydes

Table 2. Evaluation of the Michael acceptors and third electrophiles.[a]



Entry	Michael acceptor	Aldehyde	Third electrophile	Product Yield
1			 1.0 equiv.	 90% **11**
2			 1.0 equiv.	 75% **12**
3			Boc_2O 1.2 equiv.	 80% **13**
4			Boc_2O 1.2 equiv.	 86% **14**
5			Boc_2O 1.2 equiv.	 5:1 *dr* 84% **15**
6			 1.0 equiv.	 2:1 *dr* 90% **16**
7			 1.0 equiv.	 87% **17**
8			 1.0 equiv.	 83% **18**
9			$ClSi(iPr)_3$ 1.2 equiv.	 * 92% **19**
10			 1.0 equiv.	 * 85% **20**
11			 1.0 equiv.	89% **21**
12			1.0 equiv.	91% **22**

[a] All reactions were conducted under a nitrogen atmosphere; *No hydrogen peroxide added.

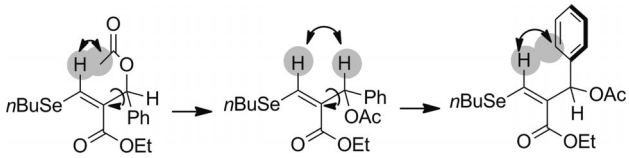


Figure 1. Key NOE enhancements for compound **20** double bond geometry elucidation.

led to the expected product in high yields (Table 2, Entries 11 and 12, respectively) under the same reaction conditions.

Conclusions

In conclusion, we have developed a Michal/aldol/*O*-functionalization/selenoxide elimination tandem protocol for the one-pot synthesis of important classes of MBH derivatives. The methodology proved to be quite general in terms of the structure and the functionalization of the Michael acceptors including those containing a methyl group at the β position. Both alkyl and aryl nonactivated aldehydes behave equally well leading to the Michael/aldol intermediates in very good yields within 45 min. Indeed, even very electron-rich aldehydes behave equally well. The addition of a third electrophile is optional and allows the preparation of densely functionalized products in a one-pot manner from commercially available starting materials. The starting selenolate nucleophile can be easily prepared in situ and is fully compatible with aldehydes, acting specifically as a Michael nucleophile, which drives the tandem Michael/aldol sequence. Another important feature to be mentioned is the fact that the whole procedure is odorless. Nevertheless, *n*-butylselenides like **2**, **19**, and **20** (or the corresponding alcohols, before *O*-functionalization) show absolutely no unpleasant smell like smaller selenides and disselenides and can be easily manipulated without any discomfort.

Last but not least, it must be noted that the use of a selenolate as the nucleophile is highly appealing, especially because at the end of the transformation it can be maintained on the structure of the product or easily eliminated by a very ecofriendly oxidant reagent (H_2O_2), resulting in the MBH derivatives in very good yields.

Experimental Section

General Remarks: All air- or moisture-sensitive reactions were carried out in dried (>100 °C) glassware under a nitrogen atmosphere. Dried solvents were distilled before use: THF was distilled from Na/benzophenone. The products were purified by flash chromatography on silica gel columns (Macherey-Nagel 60, 0.063–0.2 mm). Mixtures of ethyl acetate and hexane were generally used as chromatography eluents. Analytical TLC was performed on precoated silica gel plates (Merck silica gel 60 F254). Visualization was accomplished with UV light, vanillin, or phosphomolybdic acid solution. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-200 or 300 [200 or 300 MHz (^{1}H) and 50 or 75 MHz (^{13}C)] spectrometer in $CDCl_3$. Chemical shifts are reported in ppm (δ) with respect to TMS, and $CHCl_3$ was used as the internal standard.

General Protocol for the One-Pot Preparation of Morita–Baylis–Hillman Derivatives: In a one-necked, 100-mL round-bottomed flask previously dried under a nitrogen atmosphere equipped with a rubber septa and a magnetic stirring bar, containing elemental selenium (3 mmol, 0.2370 g) was added dry THF (45 mL). To the resulting suspension was added *n*BuLi (2 M in hexanes, 1.5 mL) dropwise under stirring and at room temperature (a light tan solution was produced). This solution was then cooled to –75 °C by using a dry ice/ethanol mixture followed by the addition of the desired aldehyde (3 mmol, 1 equiv.). Three minutes later, the appropriated Michael acceptor (3 mmol, 1 equiv.) was added dropwise. After 10 min under stirring at –75 °C the cryogenic bath was removed, and the solution was left to warm back to room temperature, followed by the slow addition of the third electrophile (1 equiv. for acid chlorides and 1.2 equiv. all others). The solution was kept under stirring for an additional 5 min (complete consumption of the intermediate alkoxide was followed by TLC). In those cases in which the selenoxide elimination was performed, 5 min after the addition of the third electrophile the system was opened and 2 mL (18 mmol, 6 equiv.) of hydrogen peroxide solution (30% v/v) was added in one portion. The solution was kept under stirring for an additional 10 min, and then followed by the addition of an ammonium chloride saturated solution (20 mL). After separation, the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The resulting organic phases were combined and dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography (silica gel; hexanes/ethyl acetate, 9:1). All the products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. The selenides were also characterized by ^{77}Se NMR spectroscopy. All new compounds were characterized by HRMS.

3-(Butylselanyl)-2-cyano-1-phenylpropyl 3-Methylbutanoate (2): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.32 (m, 4 H), 5.98 (dd, J = 11.7, 6.0 Hz, 1 H), 3.39 (ddd, J = 7.8, 6.9, 6.0 Hz, 1 H), 2.71–2.58 (m, 3 H), 2.32–2.25 (m, 2 H), 2.13 (dddd, J = 13.2, 7.6, 6.6, 2.5 Hz, 1 H), 1.67–1.54 (m, 2 H), 1.46–1.30 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.70, 136.84, 135.53, 129.51, 129.34, 129.12, 128.98, 127.39, 126.80, 118.77, 118.71, 74.00, 43.49, 41.28, 40.12, 32.59, 32.54, 25.93, 25.55, 25.41, 23.06, 22.62, 21.36, 20.65, 13.75 ppm. ^{77}Se NMR (75 MHz, $CDCl_3$) δ: 169.87, 168.28 ppm. IR (KBr): $\tilde{\nu}$ = 700, 754, 1001, 1033, 1093, 1118, 1165, 1251, 1292, 1369, 1465, 1743, 1815, 2362, 2873, 2931 cm^{-1}. HRMS: calcd. for $C_{19}H_{27}NNaO_2Se$ 404.1104; found 404.1107.

2-Cyano-1-phenylallyl 3-Methylbutanoate (5): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (d, J = 1.0 Hz, 5 H), 6.35 (t, J = 1.1 Hz, 1 H), 6.08 (d, J = 1.0 Hz, 1 H), 6.01 (d, J = 1.3 Hz, 1 H), 2.35–2.28 (m, 2 H), 2.26–2.06 (m, 1 H), 0.96 (dd, J = 6.5, 0.9 Hz, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.45, 135.77, 132.03, 129.21, 128.95, 126.96, 123.42, 116.23, 74.15, 43.28, 25.77, 22.39 ppm. IR (KBr): $\tilde{\nu}$ = 667, 700, 750, 960, 1010, 1093, 1118, 1165, 1182, 1249, 1290, 1369, 1456, 1467, 1496, 1743, 2229, 2360, 2873, 2931, 2960, 3035, 3066 cm^{-1}. HRMS: calcd. for $C_{15}H_{17}NNaO_2$ 266.1157; found 266.1156.

Methyl 2-Methylene-5-phenyl-3-[(3-phenylpropanoyl)oxy]pentanoate (12): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.06 (m, 10 H), 6.23 (dd, J = 0.5 Hz, 1 H), 5.72–5.55 (m, 2 H), 3.74 (s, 3 H), 2.95 (t, J = 7.7 Hz, 2 H), 2.69–2.55 (m, 4 H), 2.14–1.87 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.77, 165.63, 141.17, 140.31, 139.85, 128.54, 128.40, 128.35, 128.32, 126.36, 125.98, 125.35, 71.62, 51.99, 35.84, 35.83, 31.72, 30.91 ppm. IR (film): $\tilde{\nu}$ = 699, 750, 817, 959, 1030, 1077, 1142, 1198, 1248, 1273, 1295, 1354, 1364, 1438, 1454, 1495, 1603, 1632, 1737, 2861, 2930, 2951, 3002, 3027,

3062, 3086 cm^{-1}. HRMS: calcd. for $C_{22}H_{24}NaO_4$ 375.1572; found 375.1568.

(*E*/*Z*)-2-Cyano-1-phenylbut-2-en-1-yl Hexanoate (7): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.32 (m, 7 H), 6.63–6.52 (m, 2 H), 6.34–6.30 (m, 1 H), 2.43 (dtd, J = 13.4, 7.5, 3.9 Hz, 3 H), 2.07–2.01 (m, 4 H), 1.73–1.61 (m, 2 H), 1.32 (dddt, J = 9.5, 6.6, 4.7, 3.5 Hz, 6 H), 0.93–0.85 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.53, 172.26, 145.82, 145.46, 136.53, 128.74, 126.58, 126.21, 117.12, 116.76, 116.61, 115.08, 74.49, 69.05, 34.22, 34.13, 31.12, 24.43, 22.19, 16.98, 14.84, 13.80 ppm. IR (film): $\tilde{\nu}$ = 699, 735, 835, 866, 972, 1001, 1093, 1108, 1159, 1236, 1271, 1380, 1453, 1495, 1640, 1743, 2222, 2862, 2872, 2932, 2957, 3034, 3065, 3090 cm^{-1}. HRMS: calcd. for $C_{17}H_{21}NNaO_2$ 294.1470; found 294.1470

Methyl 3-Acetoxy-2-methylenenonanoate (11): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.34–6.19 (m, 1 H), 5.76 (t, J = 1.1 Hz, 1 H), 5.61 (ddd, J = 8.1, 4.4, 1.1 Hz, 1 H), 3.78 (s, 3 H), 2.08 (s, 3 H), 1.46–1.11 (m, 10 H), 0.91–0.85 (m, 4 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.89, 165.73, 140.26, 124.92, 71.82, 51.86, 34.25, 31.61, 28.86, 25.23, 22.51, 21.00, 13.98 ppm. IR (film): $\tilde{\nu}$ = 604, 637, 726, 817, 855, 919, 964, 1033, 1063, 1118, 1157, 1197, 1236, 1273, 1292, 1370, 1439, 1459, 1633, 1725, 1747 cm^{-1}. HRMS: calcd. for $C_{13}H_{22}NaO_4$ 265.1415; found 265.1407.

2-Cyano-5-methylhex-1-en-3-yl 3-Methylbutanoate (8): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.02 (d, J = 0.4 Hz, 1 H), 6.00 (d, J = 0.8 Hz, 1 H), 5.37 (ddt, J = 8.8, 5.6, 0.7 Hz, 1 H), 2.25–2.21 (m, 2 H), 2.12 (ddq, J = 13.2, 7.4, 6.6 Hz, 1 H), 1.77 (ddd, J = 13.6, 8.8, 6.1 Hz, 1 H), 1.66 (dsept, J = 7.8, 6.5 Hz, 1 H), 1.59–1.56 (m, 1 H), 0.98–0.93 (m, 12 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.02, 132.42, 123.33, 116.21, 71.51, 43.34, 41.78, 25.73, 24.33, 22.59, 22.33, 22.31, 22.04 ppm. IR (film): $\tilde{\nu}$ = 947, 994, 1060, 1092, 1117, 1166, 1183, 1249, 1293, 1370, 1389, 1468, 1742, 2227, 2874, 2934, 2961 cm^{-1}. HRMS: calcd. for $C_{13}H_{21}NNaO_2$ 246.1470; found 246.1467.

2-Cyano-1-phenylallyl Acetate (6): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 5 H), 6.33 (t, J = 1.2 Hz, 1 H), 6.04 (d, J = 1.0 Hz, 1 H), 5.98 (d, J = 1.4 Hz, 1 H), 2.15 (s, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.31, 135.71, 132.08, 129.25, 128.96, 126.98, 123.20, 116.21, 74.38, 20.91 ppm. IR (film): $\tilde{\nu}$ = 700, 743, 856, 918, 962, 1027, 1226, 1372, 1454, 1496, 1749, 2229, 2938, 3035, 3066, 3112 cm^{-1}. CAS: 143165-00-8.

2-Cyano-5-methylhex-1-en-3-yl Acetate (9): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.03 (d, J = 0.6 Hz, 2 H), 6.00 (d, J = 0.9 Hz, 2 H), 5.36 (ddt, J = 8.7, 5.7, 0.7 Hz, 2 H), 2.10 (s, 6 H), 1.76 (ddd, J = 13.6, 8.7, 6.1 Hz, 2 H), 1.70–1.61 (m, 2 H), 1.60–1.53 (m, 1 H), 0.95 (dd, J = 6.5, 1.6 Hz, 13 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.92, 132.53, 123.17, 116.20, 71.80, 41.73, 24.34, 22.55, 22.13, 20.95 ppm. IR (film): $\tilde{\nu}$ = 612, 949, 1023, 1061, 1123, 1229, 1372, 1468, 1749, 2227, 2873, 2934, 2961 cm^{-1}. CAS: 853195-08-1.

2-Cyano-5-methylhex-1-en-3-yl 3-Phenylpropanoate (10): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 7.21–7.18 (m, 4 H), 5.96 (s, 1 H), 5.89 (d, J = 0.9 Hz, 1 H), 5.37–5.32 (m, 1 H), 2.95 (t, J = 7.7 Hz, 2 H), 2.70–2.66 (m, 2 H), 1.76–1.68 (m, 1 H), 1.59–1.49 (m, 2 H), 0.92–0.89 (m, 7 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.82, 140.00, 132.48, 128.54, 128.28, 126.40, 123.10, 116.21, 71.76, 41.75, 35.75, 30.81, 24.27, 22.62, 22.06 ppm. IR (film): $\tilde{\nu}$ = 699, 751, 949, 986, 1061, 1077, 1123, 1148, 1242, 1291, 1370, 1454, 1468, 1497, 1606, 1742, 2226, 2872, 2933, 2959, 3029, 3064, 3087, 3109 cm^{-1}. HRMS: calcd. for $C_{17}H_{21}NNaO_2$ 294.1470; found 294.1484.

(*Z*)-Ethyl 2-[Acetoxy(phenyl)methyl]-3-(butylselanyl)acrylate (19): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56 (d, J = 1.0 Hz, 1 H), 7.41–7.21 (m, 5 H), 6.72 (d, J = 1.0 Hz, 1 H), 4.20 (qd, J = 7.1, 3.3 Hz, 2 H), 2.65 (t, J = 7.3 Hz, 2 H), 2.11 (s, 3 H), 1.77–1.55 (m, 1 H), 1.50–1.28 (m, 2 H), 1.22 (t, J = 7.1 Hz, 3 H), 0.97–0.80 (m, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.26, 165.70, 147.14, 138.37, 128.20, 127.89, 127.03, 127.00, 73.77, 60.68, 32.56, 28.75, 22.44, 21.01, 14.01, 13.42 ppm. ^{77}Se NMR (38 MHz, $CDCl_3$): δ = 371.36 ppm. IR (KBr): $\tilde{\nu}$ = 700, 760, 970, 1024, 1107, 1228, 1292, 1371, 1454, 1573, 1693, 1745, 2362, 2870, 2927, 2958 cm^{-1}. HRMS: calcd. for $C_{18}H_{24}NaO_4Se$ 407.0737; found 407.0744.

2-Cyano-1-phenylallyl 3-Phenylpropanoate (3): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5 H), 7.27–7.22 (m, 2 H), 7.20–7.12 (m, 3 H), 6.31 (d, J = 1.2 Hz, 1 H), 5.97 (d, J = 1.0 Hz, 1 H), 5.85 (d, J = 1.3 Hz, 1 H), 2.99–2.94 (m, 2 H), 2.80–2.68 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.23, 139.99, 135.68, 132.04, 129.27, 128.99, 128.63, 128.34, 127.01, 126.48, 123.14, 116.24, 74.43, 35.78, 30.79 ppm. IR (film): $\tilde{\nu}$ = 699, 751, 848, 955, 1001, 1028, 1079, 1144, 1190, 1239, 1372, 1412, 1454, 1496, 1586, 1603, 1624, 1745, 2228, 2864, 2932, 3030, 3063, 3087, 3109 cm^{-1}. HRMS: calcd. for $C_{19}H_{17}NNaO_2$ 314.1157; found 314.1152.

1-Phenyl-2-(phenylsulfonyl)allyl Acetate (17): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.71 (m, 2 H), 7.61–7.40 (m, 4 H), 7.27–7.14 (m, 5 H), 6.67 (dd, J = 0.4 Hz, 1 H), 6.65–6.62 (m, 1 H), 5.97 (t, J = 1.0 Hz, 1 H), 1.89 (d, J = 0.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.84, 150.08, 139.52, 136.12, 133.43, 129.03, 128.75, 128.57, 128.31, 128.13, 127.28, 71.30, 20.68 ppm. IR (film): $\tilde{\nu}$ = 534, 562, 572, 597, 630, 688, 698, 750, 780, 845, 909, 920, 961, 991, 1023, 1081, 1135, 1167, 1225, 1307, 1316, 1372, 1447, 1495, 1585, 1746, 2933, 3033, 3065 cm^{-1}. HRMS: calcd. for $C_{17}H_{16}NaO_4S$ 339.0667; found 339.0670.

2-Cyano-1-cyclohexylallyl Benzoate (16): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12–8.05 (m, 2 H), 7.62–7.55 (m, 1 H), 7.50–7.43 (m, 2 H), 6.10 (s, 1 H), 6.03 (d, J = 0.9 Hz, 1 H), 5.31 (d, J = 7.9 Hz, 1 H), 2.00–1.90 (m, 2 H), 1.85–1.67 (m, 4 H), 1.34–1.02 (m, 5 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.43, 133.46, 133.42, 129.77, 129.47, 128.56, 121.91, 116.48, 77.81, 40.07, 28.85, 28.25, 26.07, 25.63, 25.51 ppm. IR (film): $\tilde{\nu}$ = 712, 976, 1026, 1069, 1107, 1177, 1270, 1316, 1451, 1601, 1723, 2226, 2855, 2931 cm^{-1}. HRMS: calcd. for $C_{17}H_{19}NNaO_2$ 292.1313; found 292.1308.

(*Z*)-Ethyl 3-(Butylselanyl)-2-{phenyl[(triisopropylsilyl)oxy]methyl}-but-2-enoate (18): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.17 (m, 5 H), 6.29 (q, J = 0.9 Hz, 1 H), 4.30 (qd, J = 7.1, 4.5 Hz, 2 H), 2.74–2.57 (m, 2 H), 2.25 (s, 3 H), 1.67–1.55 (m, 2 H), 1.49–1.37 (m, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.22–1.12 (m, 6 H), 1.10–1.08 (m, 14 H), 0.91 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.39, 156.42, 144.58, 130.48, 127.76, 126.15, 125.37, 70.76, 60.65, 31.27, 24.67, 23.17, 21.76, 18.06, 17.93, 17.68, 14.32, 13.62, 12.31, 12.24 ppm. ^{77}Se NMR (38 MHz, $CDCl_3$): δ = 431.88 ppm. IR (KBr): $\tilde{\nu}$ = 580, 678, 734, 775, 837, 883, 1058, 1093, 1161, 1246, 1369, 1465, 1550, 1685, 2357, 2866, 2937 cm^{-1}. HRMS: calcd. for $C_{26}H_{44}NaO_3SeSi$ 535.2122; found 535.2113.

Methyl 3-[(*tert*-butoxycarbonyl)oxy]-4-methyl-2-methylenepentanoate (13): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.39 (d, J = 1.0 Hz, 2 H), 5.84 (t, J = 1.1 Hz, 2 H), 5.32 (dd, J = 5.7, 1.1 Hz, 2 H), 3.82 (s, 6 H), 2.16–1.98 (m, 2 H), 1.51 (s, 1 H), 0.99–0.94 (m, 12 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.01, 153.05, 139.55, 125.91, 82.12, 78.71, 52.01, 31.78, 27.80, 18.79, 17.11 ppm. IR (KBr): $\tilde{\nu}$ = 792, 817, 862, 956, 1072, 1122, 1165, 1255, 1280, 1369, 1462, 1629, 1745, 1362, 1881, 1974 cm^{-1}. HRMS: calcd. for $C_{13}H_{22}NaO_5$ 281.1364; found 281.1359.

Methyl 2-{[(*tert*-butoxycarbonyl)oxy](phenyl)methyl}acrylate (14): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45–7.23 (m, 5 H), 6.48 (dd, J

= 1.4, 0.9 Hz, 1 H), 6.41 (t, J = 0.8 Hz, 1 H), 5.92 (dd, J = 1.4, 0.8 Hz, 5 H), 3.71 (s, 3 H), 1,45 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.39, 152.41, 139.69, 137.53, 128.47, 127.64, 125.85, 82.63, 75.82, 52.00, 27.76 ppm. IR (KBr): $\tilde{\nu}$ = 698, 765, 864, 974, 1091, 1155, 1257, 1276, 1296, 1369, 1435, 1631, 1739, 2360, 2978 cm^{-1}. CAS: 956833-12-8.

Benzyl (2-Cyano-1-phenylallyl)carbonate (4): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.33 (m, 10 H), 6.17 (t, J = 1.2 Hz, 1 H), 6.08 (dd, J = 6.5, 1.2 Hz, 2 H), 5.18 (d, J = 2.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.95, 134.63, 131.98, 130.20, 129.53, 129.01, 128.77, 128.67, 128.40, 127.03, 122.75, 115.95, 77.98, 70.39 ppm. IR (KBr): $\tilde{\nu}$ = 698, 755, 785, 911, 956, 1252, 1384, 1456, 1497, 1754, 2229, 2956, 3036, 3066, 3090, 3111 cm^{-1}. HRMS: calcd. for $C_{18}H_{15}NNaO_3$ 316.0949; found 316.0948.

(*E*/*Z*)-Methyl 2-[Acetoxy(phenyl)methyl]but-2-enoate (20): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H), 7.19 (q, J = 7.4 Hz, 1 H), 6.99 (s, 1 H), 6.71 (p, J = 1.2 Hz, 1 H), 6.26 (qd, J = 7.2, 1.3 Hz, 1 H), 3.73 (d, J = 0.5 Hz, 3 H), 2.20 (s, 3 H), 2.13 (s, 3 H), 2.11–2.05 (m, 3 H), 2.01 (d, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.93, 169.51, 166.29, 142.72, 139.38, 138.56, 138.38, 132.14, 131.76, 128.35, 128.25, 128.06, 127.43, 127.29, 125.83, 74.42, 70.75, 51.81, 51.36, 21.08, 20.92, 15.55, 14.84 ppm. IR (KBr): $\tilde{\nu}$ = 698, 734, 916, 1024, 1145, 1234, 1369, 1436, 1741, 2360, 2954 cm^{-1}. HRMS: calcd. for $C_{14}H_{16}NaO_4$ 271.0946; found 271.0949.

(*E*/*Z*)-Methyl 2-{[(*tert*-butoxycarbonyl)oxy](phenyl)methyl}but-2-enoate (15): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46–7.29 (m, 5 H), 7.22 (q, J = 7.4 Hz, 1 H), 6.81 (s, 1 H), 6.52 (t, J = 1.3 Hz, 1 H), 6.32 (qd, J = 7.2, 1.2 Hz, 1 H), 3.75 (s, 3 H), 2.09 (dd, J = 7.3, 1.2 Hz, 3 H), 2.02 (d, J = 7.5 Hz, 3 H), 1.53 (s, 9 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.47, 166.22, 152.89, 152.48, 142.90, 140.02, 138.46, 138.21, 131.72, 128.35, 128.23, 128.07, 127.47, 127.21, 125.90, 82.38, 73.55, 51.89, 51.36, 27.75, 15.57, 14.87 ppm. IR (KBr): $\tilde{\nu}$ = 696, 744, 887, 1091, 1163, 1255, 1280, 1369, 1438, 1745, 2360, 2978 cm^{-1}. HRMS: calcd. for $C_{17}H_{22}NaO_5$ 329.1365; found 329.1369.

Ethyl 2-[Acetoxy(3,4,5-trimethoxyphenyl)methyl]acrylate (22): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.65 (d, J = 1.2 Hz, 1 H), 6.61 (s, 2 H), 6.42 (d, J = 1.0 Hz, 1 H), 5.85 (t, J = 1.2 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 3.86 (d, J = 3.9 Hz, 9 H), 2.15 (s, 3 H), 1.26 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.38, 164.92, 153.10, 139.70, 137.88, 133.20, 125.41, 104.77, 73.13, 60.95, 60.72, 56.04, 21.10, 14.02 ppm. IR (KBr): $\tilde{\nu}$ = 831, 1029, 1124, 1232, 1330, 1369, 1423, 1462, 1504, 1591, 1631, 1714, 1743, 2330, 2362, 2835, 2943, 2985 cm^{-1}. HRMS: calcd. for $C_{17}H_{22}NaO_7$ 361.1263; found 361.1257.

Ethyl 2-{Acetoxy(benzo[*d*][1,3]dioxol-5-yl)methyl}acrylate (21): ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.88 (tt, J = 2.0, 1.2 Hz, 2 H), 6.80 (dd, J = 7.8, 0.6 Hz, 1 H), 6.63 (t, J = 1.3 Hz, 1 H), 6.42 (t, J = 1.0 Hz, 1 H), 5.98 (s, 2 H), 5.88 (dd, J = 1.6, 1.0 Hz, 1 H), 4.26–4.13 (m, 2 H), 2.13 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.25, 169.35, 164.88, 147.58, 139.77, 131.54, 128.64, 125.05, 121.73, 108.09, 101.13, 72.92, 60.93, 21.08, 14.00 ppm. IR (KBr): $\tilde{\nu}$ = 731, 808, 862, 929, 1039, 1097, 1145, 1228, 1367, 1444, 1487, 1504, 1631, 1720, 1745, 2358, 2904, 2980 cm^{-1}. HRMS: calcd. for $C_{15}H_{16}NaO_6$ 315.0845; found 315.0839.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H NMR, ^{13}C NMR, and ^{77}Se NMR spectra.

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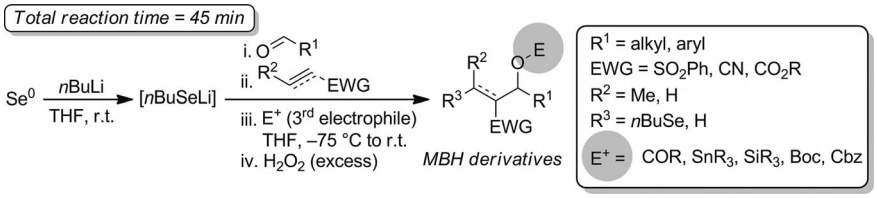

Here we describe a one-pot, fast, and high-yielding methodology for the synthesis of different Morita–Baylis–Hillman derivatives by a four-component cascade reaction. The cascade is based on a Michael/aldol/*O*-functionalization/selenoxide elimination sequence. This protocol completely avoids the manipulation of selenium species with an unpleasant odor.

Keywords: Multicomponent reactions / Domino reactions / Michael addition / Aldol reactions / Selenium

