

An Efficient Molybdenum(VI)-Catalyzed Direct Substitution of Allylic Alcohols with Nitrogen, Oxygen, and Carbon Nucleophiles

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Direct nucleophilic substitution of allylic alcohols with various nitrogen, oxygen, and carbon nucleophiles catalyzed by $\text{MoO}_2(\text{acac})_2$ was realized. The corresponding products were obtained in moderate-to-excellent yields. Studies of the reac-

tion mechanism showed that a carbenium intermediate was formed in the transition state.

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Introduction

With the rapid development of drug synthesis, nucleophilic substitution of alcohols has attracted a considerable amount of attention from organic chemists for recent years.^[1] However, because of the poor leaving ability of the hydroxy group, this process has been largely restricted to multistep synthesis: the hydroxy group must first be transformed into a better leaving group, such as halide, carboxylate, carbonates, phosphonate, or sulfonate, and so on, and then treated with the corresponding nucleophiles in the presence of a stoichiometric amount of base.^[2] The Tsuji–Trost-type reaction is a powerful and versatile method to effect allylic substitution catalyzed by palladium.^[3,4] As it is considered an ideal and more efficient way, the direct substitution of alcohols has emerged as an attractive area of research. Very recently, several attempts have been carried out to perform this transformation catalyzed by Lewis or Brønsted acids, including InCl_3 ,^[5] FeCl_3 ,^[6] $\text{Bi}(\text{OTf})_3$,^[7] $\text{Yb}(\text{OTf})_3$,^[8] $\text{Cu}(\text{BF}_4)_2$,^[9] AuCl_3 ,^[10] and *p*-toluenesulfonic acid monohydrate (PTS),^[11] under different conditions. Despite the impressive progress, the scope of nucleophiles has been restricted to a specific catalyst. Thus, the development of an alternative catalytic system that is versatile for a wide range of nucleophiles is desirable.

Molybdenum complexes constitute a family of significant compounds in chemistry. The alkylidene complexes of molybdenum (Schrock catalyst) can be employed as effective catalysts for alkene and alkyne metathesis.^[12] Allylic alkylation catalyzed by molybdenum(II) and molybdenum(0) complexes is also a well-established methodology in organic synthesis.^[1c,13] Dioxido complexes dominate the chemistry of molybdenum(VI), and their prevalence, ease of synthesis, and chemical attributes have led to their exploitation as models for enzymes and surface oxides, sensors, and drug targets.^[14] However, most of the applications of (dioxido)-molybdenum complexes in organic synthesis are focused on oxidation^[14c,15] and reduction.^[16] Very recently, we found the chiral *salan*- Mo^{VI} -dioxido complex could be explored as an effective precatalyst in the asymmetric pinacol coupling reaction of aromatic aldehydes.^[17] As a continuation of our efforts to exhibit the diversity of reactions catalyzed by (dioxido)molybdenum(VI) complexes, herein we wish to report the direct nucleophilic substitution of allylic alcohols with various nucleophiles catalyzed by $\text{MoO}_2(\text{acac})_2$.

Results and Discussion

Reactions with Nitrogen and Oxygen Nucleophiles

Initially, we studied the nucleophilic substitution of 1,3-diphenylprop-2-en-1-ol (**1a**) with the less nucleophilic formamide (**2a**) by using $\text{MoO}_2(\text{acac})_2$ (10 mol-%) as the catalyst (Table 1), and the desired product could be obtained in 47% (Table 1, Entry 1). An increase in activity was observed with NH_4PF_6 (10 mol-%) as additive (Table 1, Entry 2; 68% yield), whereas NH_4PF_6 alone showed no catalytic activity (Table 1, Entry 3). Investigations into the optimum solvent for this reaction suggested that acetonitrile is the best choice (Table 1, Entries 2 and 4–7). A drop in reac-

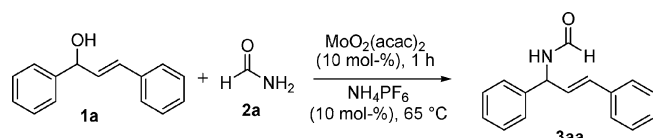
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tivity was observed when toluene was used (Table 1, Entry 4), and no product was obtained as for CH_2Cl_2 or dioxane (Table 1, Entries 5 and 6). Decreasing the temperature and the catalyst loading would prolong the reaction time.

Table 1. Nucleophilic substitution of 1,3-diphenylprop-2-en-1-ol (**1a**) with formamide (**2a**) under different conditions.^[a]



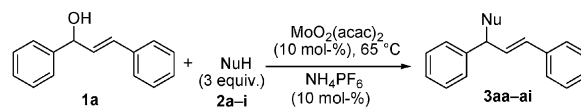
Entry	Catalyst	Additive	Solvent	Yield [%] ^[b]
1	$\text{MoO}_2(\text{acac})_2$	–	CH_3CN	47
2	$\text{MoO}_2(\text{acac})_2$	NH_4PF_6	CH_3CN	68
3	–	NH_4PF_6	CH_3CN	no reaction
4	$\text{MoO}_2(\text{acac})_2$	NH_4PF_6	toluene	30
5	$\text{MoO}_2(\text{acac})_2$	NH_4PF_6	CH_2Cl_2	– ^[c]
6	$\text{MoO}_2(\text{acac})_2$	NH_4PF_6	dioxane	trace
7	$\text{MoO}_2(\text{acac})_2$	NH_4PF_6	CH_3NO_2	68

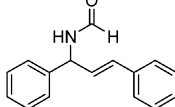
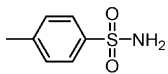
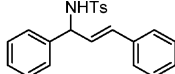
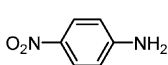
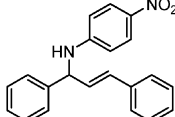
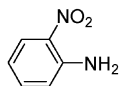
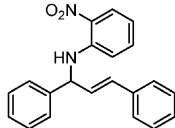
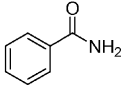
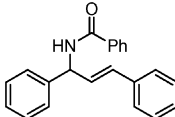
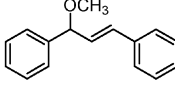
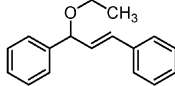
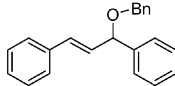
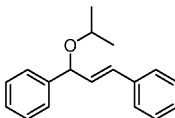
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mL), $\text{MoO}_2(\text{acac})_2$ (10 mol-%), NH_4PF_6 (10 mol-%) in solvent (2 mL). [b] Isolated yield. [c] Only oxidative product was detected.

On the basis of the optimal conditions established, we examined the nucleophilic substitution of **1a** with several nitrogen nucleophiles. The results are shown in Table 2 (Entries 1–5). To our delight, *p*-toluenesulfonamide (**2b**), 4-nitroaniline (**2c**), and 2-nitroaniline (**2d**) provided the corresponding products in high yield within a short time (Table 2, Entries 2–4), whereas the reaction of benzamide (**2e**) needed longer reaction time and provided lower yield of the product (Table 2, Entry 5; 74%, 10 h). It should be noted that a trace amount of byproduct **3an** (ca. 5% yield) was also detected in these reactions unexpectedly, with acetylacetone as the nucleophile. This result suggested that acetylacetone partly dissociated from the molybdenum complex in the catalytic cycle and functioned as a nucleophile (vide infra).

Generally, ether formation requires alcohol and halide in the presence of an equivalent amount of strong base, whereas direct intermolecular condensation of two different alcohols is considered to be an ideal protocol. In comparison to other low-oxidation-state metal complexes, reports referring to high-oxidation-state metal–oxido complexes used for the formation of sp^3 carbon–oxygen bonds are limited.^[18] Encouraged by the results of the direct substitution of allylic alcohols with nitrogen nucleophiles, we expected that other alcohols would be probably used as nucleophiles for this transformation in the presence of $\text{MoO}_2(\text{acac})_2/\text{NH}_4\text{PF}_6$. We then explored the reaction of **1a** with different alcohols in acetonitrile. As shown in Table 2 (Entries 6–9), the reactions proceeded smoothly and corresponding allylic ethers could be obtained in high yields. This protocol provides a convenient and practical method for the synthesis of allylic ethers.

Table 2. $\text{MoO}_2(\text{acac})_2$ -catalyzed direct substitution of **1a** with nitrogen and oxygen nucleophiles.^[a]



Entry	NuH	Time [h]	Product	Yield ^[b] [%]
1 ^[c]		2a 1		3aa 68
2		2b 0.5		3ab 85
3		2c 2		3ac 87
4		2d 2		3ad 90
5		2e 10		3ae 74
6 ^[c]	CH_3OH	2f 3		3af 75
7 ^[c]	$\text{CH}_3\text{CH}_2\text{OH}$	2g 1		3ag 90
8	PhCH_2OH	2h 2		3ah 71
9 ^[c]	$(\text{CH}_3)_2\text{CHOH}$	2i 2		3ai 77

[a] Reaction conditions: **1a** (0.5 mmol), nucleophile (1.5 mmol), $\text{MoO}_2(\text{acac})_2$ (10 mol-%), NH_4PF_6 (10 mol-%) in CH_3CN (2 mL) at 65 °C for the given time (unless otherwise noted). [b] Isolated yield. [c] The amount of nucleophile used in the reaction was 1 mL.

Reactions with Carbon Nucleophiles and Other Allylic Alcohols

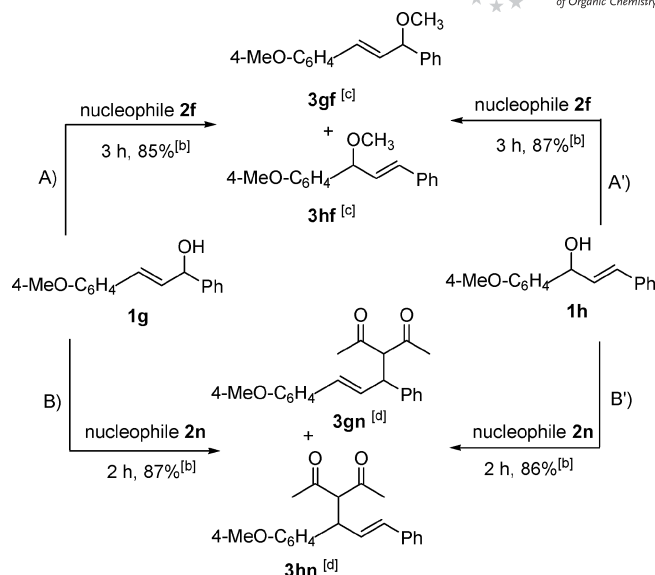
To further demonstrate the utility of this catalytic system, a number of carbon nucleophiles as well as differently substituted allylic alcohols were investigated. The results are

tion transition state. However, when simple alcohols **1e** and **1f** were employed, the reaction conversion were decreased even after 36 h, and only a mixture of regioisomers **3en** and **3fn** were observed (Table 3, Entries 9 and 10). This could be partly due to the difficulty in activating those simple allylic alcohols. Interestingly, the monoketones acetone (**2p**) and cyclohexanone (**2q**) could be transformed smoothly into corresponding products **3ap** and **3aq**, respectively, in this catalytic system (Table 3, Entries 12 and 13; 78% and 65% yield, respectively). To the best of our knowledge, as a result of their low activities, substitution reactions with the use of these simple ketones as the nucleophiles have not yet been reported, except for the Tsuji–Trost-type reaction catalyzed by palladium complexes.^[21] Therefore, $\text{MoO}_2(\text{acac})_2$ could be regarded as a highly efficient catalyst for the substitution of allylic alcohols.

Mechanism Studies

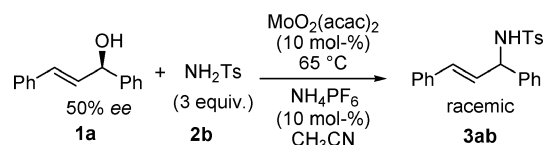
Finally, we turned our attention to the reaction mechanism. Dissymmetric allylic alcohols **1g** and **1h** were investigated under the same reactions condition. As shown in Scheme 1, the reactions of **1g** or **1h** with methanol (**2f**) generated mixtures of products **3gf** and **3hf** in a ratio^[22] of 54:46 (path A and A'). The carbon nucleophile acetylacetone (**2n**) also gave the mixture of products, though the ratio between **3gn** and **3hn** was different from that with methanol as the nucleophile (path B and B'). However, the allylic alcohol bearing an electron-withdrawing group on the aryl rings, a nitro group for example, underwent only sluggish conversion. This result suggested that the substitution proceeded through an $\text{S}_{\text{N}}1$ -like mechanism.

In order to obtain further evidence on this hypothesis, optically active alcohol **1a** with 50% *ee* was treated with **2b** under the specified reaction conditions and racemic product **3ab** was observed as anticipated (Scheme 2). Moreover, a trace amount of byproduct **3an** was also observed. It is supposed that the transition state involves coordination of allylic alcohol **1a**, which replaces acetylacetone with the mo-

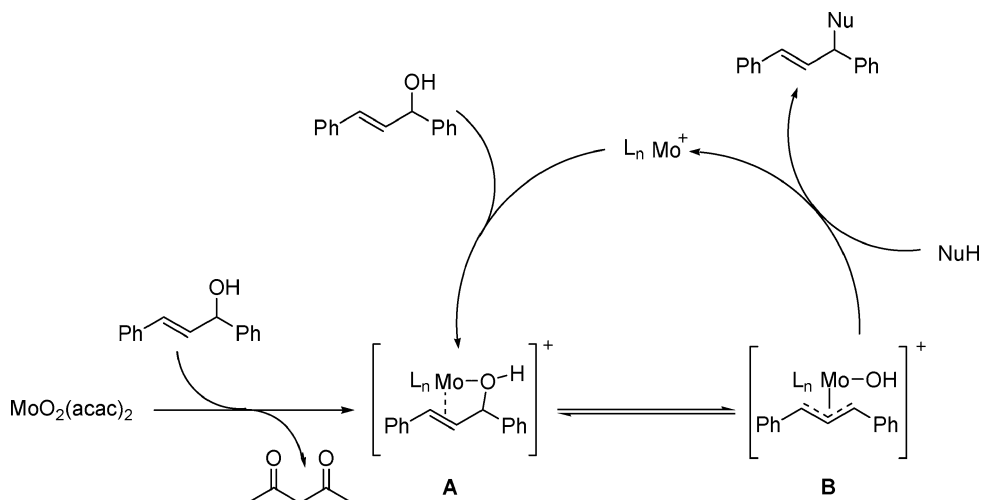


Scheme 1. $\text{MoO}_2(\text{acac})_2$ -catalyzed direct substitution of alcohols **1g** and **1h**.^[a] [a] Reaction conditions: allylic alcohol (0.5 mmol), nucleophile (1 mL), $\text{MoO}_2(\text{acac})_2$ (10 mol-%), NH_4PF_6 (10 mol-%) in CH_3CN (2 mL) at 65 °C for the given time. [b] Isolated yield. [c] The ratio between **3gf** and **3hf** is 54:46. [d] The ratio between **3gn** and **3hn** is 33:67.

lybdenum complex in the catalytic cycle (intermediate A). Attack of the nucleophile on π -allylic carbenium intermediate B, which gives rise to the corresponding product, is the driving force of the equilibrium from intermediate A to B (Scheme 3).^[23]



Scheme 2. $\text{MoO}_2(\text{acac})_2$ -catalyzed direct amination of the optically active alcohol **1a**.



Scheme 3. Proposed pathway for $\text{MoO}_2(\text{acac})_2$ -catalyzed substitution of **1a**.

Conclusions

In summary, we have developed the $\text{MoO}_2(\text{acac})_2$ -catalyzed direct substitution of allylic alcohols with a wide range of nitrogen, oxygen, and carbon nucleophiles, which proceeds with moderate-to-excellent yields. The $\text{MoO}_2(\text{acac})_2/\text{NH}_4\text{PF}_6$ combination is a versatile and highly efficient catalyst system for the substitution reaction. Studies into the reaction mechanism suggest that the molybdenum(VI) complex functioned as a Lewis acid in the transition state and a carbenium intermediate could be formed, which is different from the mechanism of allylation catalyzed by Mo^{II} or Mo^0 complexes.

Experimental Section

General: All reagents were obtained from commercial suppliers and used without further purification except as indicated below. $\text{MoO}_2(\text{acac})_2$ was readily prepared according to the literature.^[24] Dioxane was freshly distilled from sodium metal. Acetonitrile was freshly distilled from P_2O_5 . Reactions were monitored by TLC on silica-gel plates (GF254). ^1H and ^{13}C NMR spectra were recorded with a Bruker APX-300 spectrometer at room temperature in CDCl_3 as solvent. Infrared spectra were recorded with a VECTOR 22 spectrometer with pressed KBr pellets. Elemental analyses were carried out with a Perkin–Elmer 240 C elemental analyzer in the Analysis Center of Nanjing University. Mass spectra (ESI) were taken with an LCQ Classic mass spectrometer.

General Procedure for the Nucleophilic Substitution Reaction of Alcohols: To a stirred solution of $\text{MoO}_2(\text{acac})_2$ (16 mg, 0.05 mmol) and NH_4PF_6 (9 mg, 0.05 mmol) in acetonitrile (2 mL) at 65 °C was added the corresponding nucleophiles (1.5 mmol or 1 mL), and the resulting mixture was stirred for 5 min before the addition of the alcohol (0.5 mmol). The mixture was stirred at this temperature for the specified time (Tables 2 and 3) and then cooled to room temperature and directly purified by flash chromatography on silica gel to afford the corresponding product.

3aa: White solid. Yield: 80 mg, 68%. M.p. 118–119 °C. ^1H NMR (300 MHz, CDCl_3): δ = 5.89 (d, J = 6.9 Hz, 1 H), 6.18 (s, 1 H), 6.30 (dd, J = 6.3, 15.9 Hz, 1 H), 6.53 (d, J = 15.9 Hz, 1 H), 7.24 (m, 10 H), 8.27 (s, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 53.6, 126.6, 127.2, 127.9, 128.0, 128.4, 128.7, 128.9, 131.7, 136.4, 140.4, 160.4 ppm. IR (KBr): $\tilde{\nu}$ = 3238, 3042, 2869, 1676, 1655, 1544, 1491, 1383, 1259, 973, 750, 695 cm^{-1} . $\text{C}_{16}\text{H}_{15}\text{NO}$ (237.12): calcd. C 80.98, H 6.37, N 5.90; found C 80.85, H 6.42, N 5.83.

3ab:^[2b] White solid. Yield: 154 mg, 85%. M.p. 129–131 °C. ^1H NMR (300 MHz, CDCl_3): δ = 2.30 (s, 3 H), 5.08–5.17 (m, 2 H), 6.03 (dd, J = 6.6, 15.6 Hz, 1 H), 6.31 (d, J = 15.6 Hz, 1 H), 7.11–7.25 (m, 12 H), 7.64 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 21.8, 60.2, 126.9, 127.5, 127.7, 128.3, 128.6, 128.9, 129.1, 129.8, 132.5, 136.5, 138.2, 140.1, 143.7 ppm. IR (KBr): $\tilde{\nu}$ = 3350, 3030, 2960, 2923, 2855, 1633, 1516, 1488, 1313, 1258, 1077, 1032, 967, 801, 747, 699 cm^{-1} . MS (ESI): m/z (%) = 362 (100) $[\text{M} - \text{H}]^-$.

3ac:^[11a] Yellow solid. Yield: 144 mg, 87%. M.p. 136–137 °C. ^1H NMR (300 MHz, CDCl_3): δ = 4.99 (m, 1 H), 5.24 (t, J = 5.7 Hz, 1 H), 6.40 (dd, J = 6.0, 15.9 Hz, 1 H), 6.59–6.66 (m, 3 H), 7.24–7.43 (m, 10 H), 8.08 (d, J = 9.3 Hz, 2 H) ppm.

3ad: Yellow oil. Yield: 149 mg, 90%. ^1H NMR (300 MHz, CDCl_3): δ = 4.79 (d, J = 7.2 Hz, 1 H), 6.37 (d, J = 15.9 Hz, 1 H), 6.56 (dd,

J = 7.2, 15.9 Hz, 1 H), 6.73 (d, J = 8.4 Hz, 1 H), 7.31 (m, 13 H), 8.00 (s, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 53.3, 119.5, 125.7, 126.8, 127.2, 128.0, 128.9, 129.0, 129.1, 132.0, 132.4, 133.0, 136.8, 137.4, 143.1, 143.8 ppm. IR (KBr): $\tilde{\nu}$ = 3489, 3377, 3059, 3026, 2969, 2925, 1632, 1591, 1564, 1513, 1410, 1340, 1254, 1168, 1087, 969, 745, 688 cm^{-1} . MS (ESI): m/z (%) = 329 (42) $[\text{M} - \text{H}]^-$. $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2$ (330.14): calcd. C 76.34, H 5.49, N 8.48; found C 76.26, H 5.53, N 8.42.

3ae:^[7] White solid. Yield: 116 mg, 74%. M.p. 157–159 °C. ^1H NMR (300 MHz, CDCl_3): δ = 6.05 (t, J = 6.6 Hz, 1 H), 6.47 (dd, J = 5.7, 15.9 Hz, 1 H), 6.56 (m, 2 H), 7.20 (m, 13 H), 7.81 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 55.6, 127.0, 127.5, 127.6, 128.2, 129.0, 129.1, 129.2, 129.3, 132.1, 132.2, 134.7, 136.8, 141.2, 166.9 ppm. IR (KBr): $\tilde{\nu}$ = 3443, 3060, 3029, 2926, 1597, 1492, 1449, 1427, 1326, 1155, 695, 671, 560 cm^{-1} . MS (ESI): m/z (%) = 311 (85) $[\text{M} - \text{H}]^-$.

3af:^[25] Colorless oil. Yield: 84 mg, 75%. ^1H NMR (300 MHz, CDCl_3): δ = 3.37 (s, 3 H), 4.78 (d, J = 6.9 Hz, 1 H), 6.24 (dd, J = 6.9, 15.9 Hz, 1 H), 6.60 (d, J = 15.9 Hz, 1 H), 7.19 (m, 10 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 56.8, 84.7, 127.0, 127.3, 127.5, 128.1, 128.9, 130.5, 131.9, 137.0, 141.4 ppm. IR (KBr): $\tilde{\nu}$ = 3450, 3059, 2974, 2926, 1493, 1450, 1081, 965, 744, 695 cm^{-1} .

3ag:^[26] Colorless oil. Yield: 108 mg, 90%. ^1H NMR (300 MHz, CDCl_3): δ = 1.29 (t, J = 6.9 Hz, 3 H), 3.52–3.65 (m, 2 H), 4.95 (d, J = 6.9 Hz, 1 H), 6.34 (dd, J = 7.2, 15.9 Hz, 1 H), 6.64 (d, J = 15.9 Hz, 1 H), 7.28–7.42 (m, 10 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 15.7, 64.4, 82.9, 127.0, 127.2, 127.5, 128.0, 128.1, 128.9, 130.4, 131.1, 131.5, 132.0, 137.1, 142.0 ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3059, 3026, 2974, 2926, 2820, 1493, 1450, 1081, 965, 744, 696, 554 cm^{-1} .

3ah:^[27] Yellow oil. Yield: 107 mg, 71%. ^1H NMR (300 MHz, CDCl_3): δ = 4.62 (s, 2 H), 5.05 (d, J = 6.9 Hz, 1 H), 6.38 (dd, J = 6.9, 15.9 Hz, 1 H), 6.60 (d, J = 15.9 Hz, 1 H), 7.20–7.45 (m, 15 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 70.5, 82.0, 127.0, 127.4, 127.7, 128.0, 128.1, 128.8, 129.0, 130.7, 132.0, 137.0, 138.8, 141.6 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2971, 2901, 1650, 1601, 1492, 1450, 1389, 1259, 1053, 965, 740, 694 cm^{-1} .

3ai:^[26] Pale-yellow oil. Yield: 97 mg, 77%. ^1H NMR (300 MHz, CDCl_3): δ = 1.18 (d, J = 5.7 Hz, 3 H), 1.22 (d, J = 5.7 Hz, 3 H), 3.71 (m, 1 H), 5.03 (d, J = 6.9 Hz, 1 H), 6.26 (dd, J = 6.9, 15.9 Hz, 1 H), 6.55 (d, J = 15.9 Hz, 1 H), 7.15–7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 22.7, 22.8, 69.1, 80.0, 127.0, 127.3, 127.5, 127.9, 128.0, 128.9, 131.2, 131.6, 137.2, 142.4 ppm. IR (KBr): $\tilde{\nu}$ = 3449, 3059, 3026, 2970, 2927, 1600, 1493, 1450, 1374, 1298, 1120, 1047, 966, 743, 696 cm^{-1} .

3aj:^[19a] Yellow oil. Yield: 96 mg, 67%. ^1H NMR (300 MHz, CDCl_3): δ = 4.82 (d, J = 7.2 Hz, 1 H), 4.89 (s, 1 H), 6.30 (d, J = 15.6 Hz, 1 H), 6.60 (dd, J = 8.1, 15.6 Hz, 1 H), 6.76 (d, J = 8.7 Hz, 2 H), 7.08 (d, J = 8.7 Hz, 2 H), 7.20 (m, 10 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 53.7, 115.7, 126.7, 126.8, 127.7, 128.8, 128.9, 129.0, 130.2, 131.6, 133.3, 136.2, 137.7, 144.2, 154.5 ppm. IR (KBr): $\tilde{\nu}$ = 3414, 3059, 3026, 2971, 2927, 1639, 1602, 1508, 1447, 1237, 1174, 1040, 970, 833, 746, 698, 553 cm^{-1} . MS (ESI): m/z (%) = 285 (50) $[\text{M} - \text{H}]^-$.

3ak:^[11b] Yellow oil. Yield: 125 mg, 97%. ^1H NMR (300 MHz, CDCl_3): δ = 4.85 (d, J = 7.5 Hz, 1 H), 5.97 (s, 1 H), 6.17 (s, 1 H), 6.40 (d, J = 15.9 Hz, 1 H), 6.55 (dd, J = 7.5, 15.9 Hz, 1 H), 6.70 (s, 1 H), 7.19 (m, 10 H), 7.85 (s, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 48.5, 107.2, 108.5, 117.7, 126.8, 127.3, 127.9, 128.8, 129.0, 129.1, 131.5, 131.7, 133.5, 137.5, 142.6 ppm. IR (KBr): $\tilde{\nu}$ =

3430, 3058, 3025, 2360, 2339, 1597, 1492, 1449, 1090, 1027, 965, 746, 697, 538 cm⁻¹.

3al:^[11a] Colorless oil. Yield: 128 mg, 83%. ¹H NMR (300 MHz, CDCl₃): δ = 5.07 (d, J = 7.2 Hz, 1 H), 6.39 (d, J = 15.9 Hz, 1 H), 6.66 (dd, J = 7.2, 15.9 Hz, 1 H), 6.79 (s, 1 H), 7.03 (t, J = 7.2 Hz, 1 H), 7.15–7.43 (m, 13 H), 7.77 (br. s, 1 H) ppm.

3dl:^[28] Yellow oil. Yield: 47 mg, 51%. ¹H NMR (300 MHz, CDCl₃): δ = 1.78 (s, 3 H), 1.79 (s, 3 H), 3.48 (d, J = 7.2 Hz, 2 H), 5.46 (m, 1 H), 6.97 (s, 1 H), 7.13–7.23 (m, 2 H), 7.36 (d, J = 7.8 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.76 (br., 1 H) ppm.

3am: White solid. Yield: 133 mg, 80%. M.p. 61–62 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.06 (s, 6 H), 2.37 (s, 4 H), 5.26 (d, J = 6.9 Hz, 1 H), 6.38 (d, J = 15.9 Hz, 1 H), 6.95 (dd, J = 6.9, 15.9 Hz, 1 H), 7.22–7.39 (m, 10 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 28.4, 31.99, 41.90, 60.52, 116.3, 126.4, 127.4, 127.8, 128.1, 128.5, 129.0, 129.8, 130.6, 131.7, 137.3, 142.4 ppm. IR (KBr): $\tilde{\nu}$ = 3024, 2957, 1598, 1376, 1256, 746, 696 cm⁻¹. MS (ESI): m/z (%) = 331 (100) [M – H]⁺. C₂₃H₂₄O₂ (332.18): calcd. C 83.10, H 7.28; found C 82.92, H 7.33.

3an:^[11a] White solid. Yield: 131 mg, 90%. M.p. 84–85 °C. ¹H NMR (300 MHz, CDCl₃): δ = 1.92 (s, 3 H), 2.25 (s, 3 H), 4.34 (m, 2 H), 6.17 (dd, J = 5.7, 15.9 Hz, 1 H), 6.48 (d, J = 15.9 Hz, 1 H), 7.22–7.34 (m, 10 H) ppm.

3bn:^[11a] Yellow oil. Yield: 72 mg, 63%. ¹H NMR (300 MHz, CDCl₃): δ = 1.09 (d, J = 6.9 Hz, 3 H), 2.14 (s, 3 H), 2.24 (s, 3 H), 3.20–3.26 (m, 1 H), 3.70 (d, J = 10.5 Hz, 1 H), 6.00 (dd, J = 15.9, 8.7 Hz, 1 H), 6.45 (d, J = 15.9 Hz, 1 H), 7.22–7.32 (m, 5 H) ppm.

3cn:^[29] Yellow oil (keto/enol, 1:0.92). Yield: 62 mg, 57%. ¹H NMR (300 MHz, CDCl₃): δ = 2.17 (s, 6 H, enol), 2.22 (s, 6 H, keto), 2.76 (td, J = 6.9, 0.9 Hz, 2 H, keto), 3.17 (dd, J = 5.4, 1.5 Hz, 2 H, enol), 3.81 (t, J = 6.9 Hz, 1 H, keto), 6.08 (dt, J = 15.9, 7.2 Hz, 1 H, keto), 6.22 (dt, J = 15.9, 5.4 Hz, 1 H, enol), 6.36 (d, J = 15.9 Hz, 1 H, enol), 6.46 (d, J = 15.9 Hz, 1 H, keto), 7.21–7.34 (m, 10 H, keto + enol) ppm.

3ao:^[11a] Colorless oil (mixture of diastereoisomers, ca. 3:2). Yield: 156 mg, 97%. ¹H NMR (300 MHz, CDCl₃): δ = 0.98 (t, J = 6.9 Hz, 1.2 H, diast. A), 1.22 (t, J = 6.9 Hz, 1.8 H, diast. B), 2.06 (s, 1.8 H, diast. B), 2.33 (s, 1.2 H, diast. A), 3.95 (q, J = 6.9 Hz, 0.8 H, diast. A), 4.10–4.23 (m, 2 H), 4.31–4.40 (m, 1.2 H, diast. B), 6.29 (m, 1 H), 6.43 (m, 1 H), 7.24–7.32 (m, 10 H) ppm.

3ap:^[30] Pale-yellow oil. Yield: 98 mg, 78%. ¹H NMR (300 MHz, CDCl₃): δ = 2.10 (s, 3 H), 2.94 (m, 2 H), 4.07 (q, J = 6.3 Hz, 1 H), 6.35 (m, 2 H), 7.19–7.33 (m, 10 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 31.1, 44.4, 49.8, 126.6, 127.1, 127.7, 128.0, 128.9, 129.1, 130.4, 132.8, 137.5, 143.4, 207.3 ppm. IR (KBr): $\tilde{\nu}$ = 3420, 1715, 1599, 1493, 1450, 1414, 1358, 1158, 966, 745, 697, 540 cm⁻¹.

3aq:^[21] Colorless oil (mixture of diastereoisomers, ca. 1:1). Yield: 94 mg, 65%. ¹H NMR (300 MHz, CDCl₃): δ = 1.57 (m, 4 H), 1.90 (m, 2 H), 2.35 (m, 2 H), 2.86 (m, 1 H), 3.87 (dd, J = 9.0, 8.7 Hz, 0.5 H, diast. A), 3.97 (dd, J = 9.0, 8.7 Hz, 0.5 H, diast. B), 6.26–6.34 (m, 1 H), 6.43–6.48 (m, 1 H), 7.15–7.43 (m, 10 H) ppm.

3gf and 3hf: Colorless oil (**3gf/3hf**, 54:46). Data for **3gf**: ¹H NMR (300 MHz, CDCl₃): δ = 3.40 (s, 3 H), 3.81 (s, 3 H), 4.77–4.81 (m, 1 H), 6.17 (dd, J = 7.2, 15.9 Hz, 1 H), 6.59 (d, J = 15.6 Hz, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.24–7.42 (m, 7 H) ppm. Data for **3hf**: ¹H NMR (300 MHz, CDCl₃): δ = 3.38 (s, 3 H), 3.83 (s, 3 H), 4.77–4.81 (m, 1 H), 6.32 (dd, J = 7.2, 15.9 Hz, 1 H), 6.63 (d, J = 15.6 Hz, 1 H), 6.93 (d, J = 9 Hz, 2 H), 7.24–7.42 (m, 7 H) ppm. Data for the mixture: ¹³C NMR (75 MHz, CDCl₃): δ = 55.7, 56.7, 56.8, 84.3,

84.9, 114.4, 127.0, 127.3, 127.5, 128.1, 128.2, 128.4, 128.6, 128.7, 128.9, 129.8, 130.8, 131.6, 133.6, 137.1, 141.7, 159.7, 159.8 ppm.

3gn and 3hn:^[31] White solid (**3gn/3hn**, 33:67). Data for **3gn**: ¹H NMR (300 MHz, CDCl₃): δ = 1.96 (s, 3 H), 2.28 (s, 3 H), 3.81 (s, 3 H), 4.33–4.36 (m, 2 H), 6.08 (ddd, J = 1.2, 6.6, 15.9 Hz, 1 H), 6.40 (d, J = 15.9 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.19–7.32 (m, 7 H) ppm. Data for **3hn**: ¹H NMR (300 MHz, CDCl₃): δ = 1.97 (s, 3 H), 2.28 (s, 3 H), 3.81 (s, 3 H), 4.33–4.36 (m, 2 H), 6.21 (ddd, J = 3.9, 3.9, 15.6 Hz, 1 H), 6.43 (d, J = 15.6 Hz, 1 H), 6.89 (d, J = 9.0 Hz, 2 H), 7.19–7.32 (m, 7 H) ppm. Data for the mixture: ¹³C NMR (75 MHz, CDCl₃): δ = 29.8, 30.0, 48.4, 49.3, 55.3, 74.7, 114.0, 114.4, 126.4, 127.1, 127.2, 127.6, 127.7, 127.9, 128.5, 129.0, 129.4, 129.6, 131.1, 131.3, 132.0, 136.6, 140.4, 158.7, 159.3, 202.8, 203.0 ppm.

Supporting Information (see footnote on the first page of this article): ¹H NMR and 2D H–H NOESY NMR spectra for the mixtures of **3gf/3hf** and **3gn/3hn**.

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