Sequential One-Pot Combination of Multireactions through Multicatalysis: A General Approach to Rapid Assembly of Functionalized Push−Pull Olefins, Phenols, and 2-Methyl-2*H*-chromenes

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A general, sustainable and practical process for the sequential cascade one-pot synthesis of library of highly substituted push−pull olefins, phenols and 2-methyl-2*H*-chromenes was reported through multicatalysis cascade (MCC) reactions. Direct sequential one-pot combination of amine- or amino acid-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation with other reactions like amine- or amino acid-catalyzed cascade Claisen−Schmidt/iso-aromatization, Claisen−Schmidt/isomerization, Claisen−Schmidt/iso-aromatization/isomerization, Michael addition, Claisen−Schmidt/Michael, ruthenium-base-silica-catalyzed ring closing metathesis/base-induced ring-opening/benzylic oxidation/[1,7]-sigmatropic hydrogen shift, or ruthenium-base-heat-catalyzed ring closing metathesis/base-induced ring-opening/[1,7]-sigmatropic hydrogen shift reactions of alkyl acetoacetates, a variety of aldehydes and alkyl halides furnished the highly functionalized push−pull olefins, phenols and 2-methyl-2*H*-chromenes with high yields. The yields and regioselectivities were good to excellent. Evidence for a new reaction pathway involving in situ formation of novel push−pull dienamines under amine- or amino acid-catalysis is presented along with examples demonstrating the amenability of the process to MCC chemistry.

Introduction

Critical objectives in modern synthetic organic chemistry include the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically and electronically complex compounds under sustainable reaction conditions as mimicking cellular reactions. In this regard, the development of one-pot sequential combination of multicatalysis and multicomponent reaction methodologies can provide expedient access to complex products from simple starting materials.[1] Recently, amine- or amino acid-catalysis (organocatalysis) has emerged as a promising sustainable synthetic tool for the constructing combination of C−C, C−N, C−O, C−S, C−P, C−F, and/or C−H bonds in a single operation with high diastereo- and enantioselectivity in a cascade or multicomponent process.[2] Generally in organocatalysis, structurally simple and stable chiral organoamines and amino acids facilitate iminium- and enamine-based transformations with carbonyl compounds and are used as catalysts in operationally simple and environmentally friendly cascade reactions.

As part of our research program to engineer direct combination of organocatalytic multicomponent and multicatalysis reactions,[3] herein we report the organocatalytic regioselective direct cascade Claisen−Schmidt/iso-aromatization (CS/IA), Claisen−Schmidt/isomerization (CS/I), Claisen−Schmidt/iso-aromatization/isomerization (CS/IA/I), Claisen−Schmidt/Michael (CS/M), Michael addition, ring closing metathesis (RCM), base-induced ring-opening (BIRO), benzylic oxidation (BO), and [1,7]-sigmatropic hydrogen shift ([1,7]-SHS) reactions that produce highly substituted 2-arylidene or 2-alkylidene cyclohexanones (push−pull olefins) **4**, highly substituted push−pull phenols **5**, functionalized aldehydes **6**, highly functionalized (*E*)-1,3-dienes **7**, functionalized bis-enones **8**, fully functionalized benzenes **9**, functionalized benzo[*b*]oxepines **10**, functionalized (*Z*)-2-(buta-1,3-dienyl)phenols **11/12**, and highly substituted 2-methyl-2*H*-chromenes **13/14** from commercially available Hagemann's esters **1**, aldehydes **2**, allyl bromide {***1***} or propargyl bromide {***2***} and amines or amino acids **3** as shown in Scheme 1. Push−pull olefins and phenols **4/5** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[4] while functionalized 2-methyl-2*H*-chromenes **13/14** and analogues thereof have broad utility in pharmaceutical chemistry[5] and in organic synthesis (see Chart 1). Hence, their economical and environmental friendly preparation has continued to attract considerable synthetic interest in developing new methods for their syntheses.[6]

We envisioned that an amine- or amino acid would catalyze the cascade Claisen−Schmidt condensation of a variety of aldehydes **2** (Figure 1) with in situ generated push−pull dienamine (1-amino-1,3-butadiene)[7] intermediate from Hagemann's esters **1** (Figure 2) and amine/amino acid **3** to form substituted push−pull olefins (3-arylidene Hagemann's ester)

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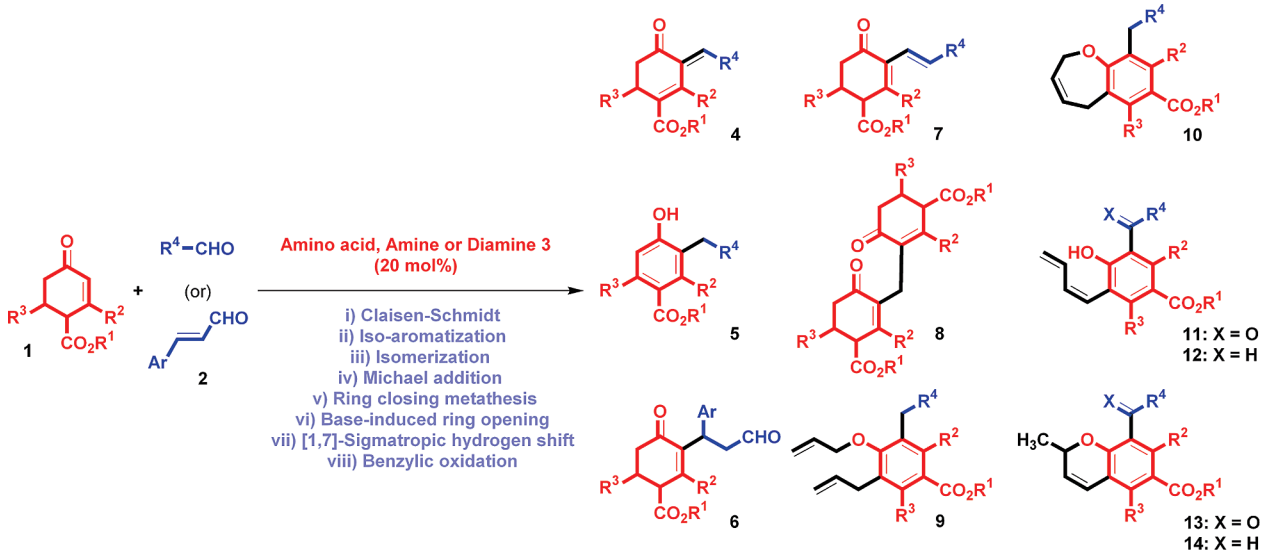
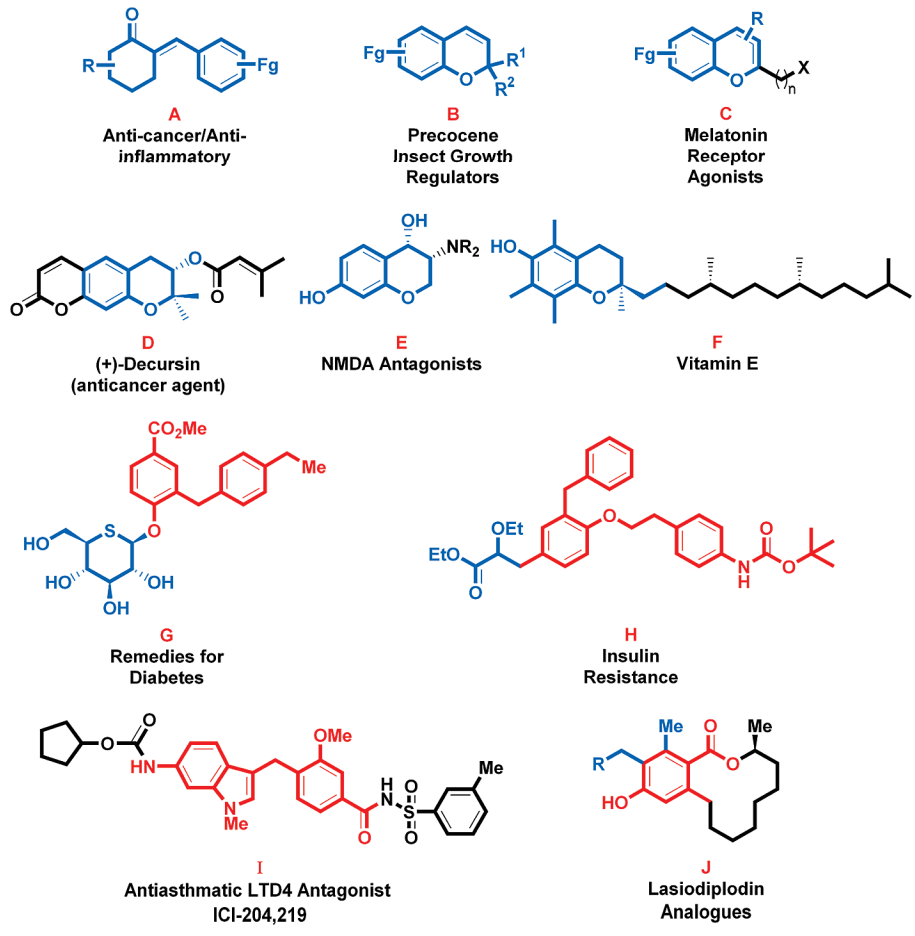
Scheme 1. Direct Organocatalytic Sequential One-pot Cascade Reactions Based on the Push-Pull Dienamine Platform



Abbreviations of Sequential Cascade Reactions Used in this Work:

Claisen-Schmidt (CS) and Claisen-Schmidt/Iso-aromatization (CS/IA)
Claisen-Schmidt/Isomerization (CS/I)
Claisen-Schmidt/Iso-aromatization/Isomerization (CS/IA/I)
Michael addition (M) and Claisen-Schmidt/Michael (CS/M)
Knoevenagel/Michael/Aldol condensation/Decarboxylation (K/M/A/DC)
Knoevenagel/Michael/Aldol condensation/Decarboxylation/Claisen-Schmidt/Iso-aromatization (K/M/A/DC/CS/IA)
Knoevenagel/Michael/Aldol condensation/Decarboxylation/Claisen-Schmidt/Iso-aromatization/Alkylation (K/M/A/DC/CS/IA/A)
Ring Closing Metathesis/Base-Induced Ring Opening/Benzylic Oxidation (RCM/BIRO/BO)
Ring Closing Metathesis/Base-Induced Ring Opening (RCM/BIRO)
[1,7]-Sigmatropic Hydrogen Shift ([1,7]-SHS)

Chart 1. Some Natural/Non-Natural Products and Pharmaceuticals Containing Cascade Compounds Obtained from Push-Pull Dienamine Chemistry



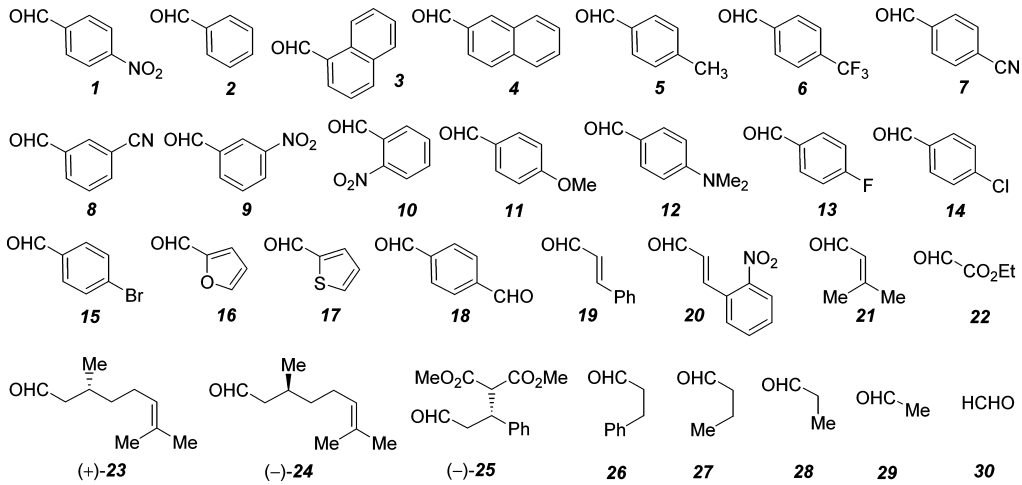


Figure 1. Diversity reagents **2**{*1*−*30*}.

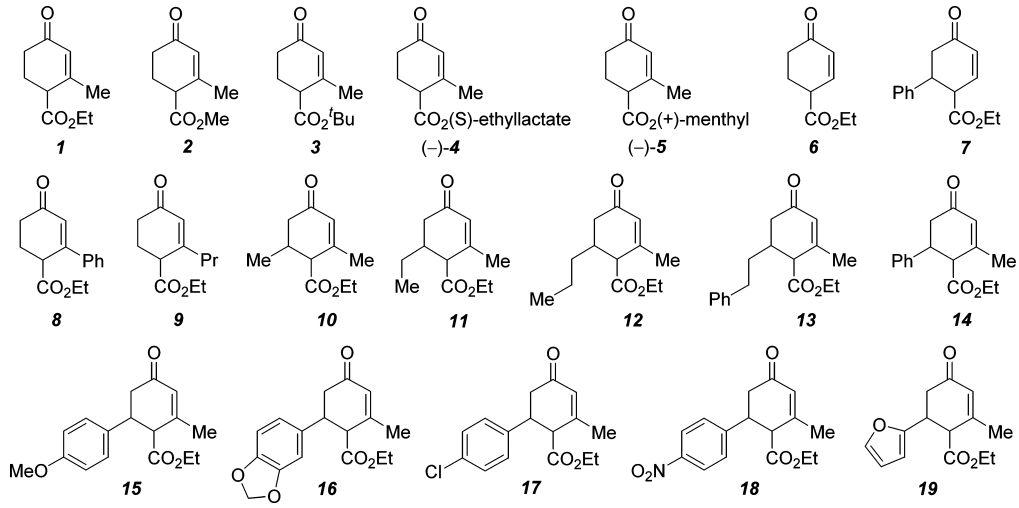


Figure 2. Diversity reagents **1**{*1*−*19*}.

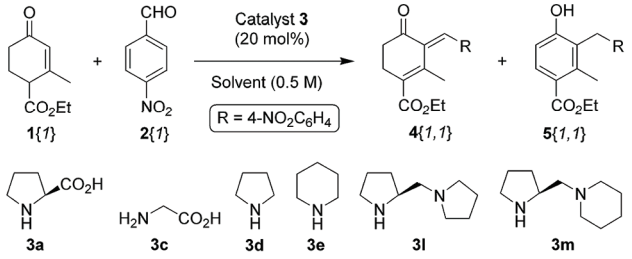
4 in a highly regioselective manner, which then undergoes iso-aromatization to produce substituted push−pull phenols **5**, isomerization to produce substituted (*E*)-1,3-dienes **7** or Michael addition with **1** to produce substituted bis-enones **8** under base-catalysis based on the electronic nature of aldehydes **2** and amines **3**. Substituted push−pull phenols **5** were transformed into the push−pull benzo[*b*]oxepines **10**, push−pull (*Z*)-2-(buta-1,3-dienyl)phenols **11/12**, and push−pull 2-methyl-2*H*-chromenes **13/14** through RCM, BIRO, BO and [1,7]-SHS reaction sequences respectively.

Results and Discussions

Direct Amino Acid- or Amine-Catalyzed Cascade Claisen−Schmidt and Claisen−Schmidt/Iso-Aromatization. Reaction Optimization. We were surprised to find that the reaction of Hagemann's ester **1**{*1*} and 4-nitrobenzaldehyde **2**{*1*} with a catalytic amount of L-proline **3a** in dimethylsulfoxide (DMSO) at 25 or 75 °C for 48 or 24 h respectively, did not furnished the expected products **4**{*1,1*} or **5**{*1,1*} as shown in Table 1, entries 1 and 2. Interestingly, the same reaction catalyzed by phenylalanine **3b** at 25 °C for 96 h furnished the Claisen−Schmidt (CS) product **4**{*1,1*} as a 1.25:1 mixture of *E*/*Z* isomers in 40% yield and without formation of cascade product **5**{*1,1*} (Table 1, entry 3). In a similar manner, reaction of **1**{*1*} with **2**{*1*} under glycine **3c**-catalysis in DMSO at 25 °C for 24 h furnished the CS product **4**{*1,1*} as a 1.25:1 mixture of *E*/*Z* isomers in 73% yield and without cascade product **5**{*1,1*} (Table 1, entry 4). Interestingly, the same reaction took longer reaction time with lesser yield in dimethylformamide (DMF) as solvent, and also CS product furnished with very poor yields in MeOH as solvent (Table 1, entries 5−6). Interestingly, the cascade reaction catalyzed by bifunctional catalyst, pyrrolidine **3d**/AcOH in DMF at 25 °C for 12 h furnished the Claisen−Schmidt/iso-aromatization (CS/IA) product **5**{*1,1*} in 30% yield and without isolation of CS product **4**{*1,1*} as shown in Table 1, entry 7.

On the basis of the result of entry 7, we screened several pyrrolidine-based catalysts **3d**−**m** by monitoring the reaction yield and regioselectivity of the cascade reaction of **1**{*1*} and **2**{*1*} in DMF/DMSO. In the cascade CS/IA reaction of **1**{*1*} and **2**{*1*} catalyzed directly by pyrrolidine **3d**, we found that the solvent had a significant effect on the rates and yields (Table 1, entries 8−14). The cascade CS/IA reaction produced the **5**{*1,1*} with good yields in aprotic dipolar solvents like DMF and DMSO, but did not furnish products **4**{*1,1*} or **5**{*1,1*} in protic polar solvents (H_2O, MeOH, EtOH, $CHCl_3$, CH_3CN), the aprotic polar solvent (THF), and in the ionic liquid [bmim]BF_4 under the pyrrolidine **3d**-catalysis (results not presented in Table 1). The amine-

Table 1. Optimization of the Direct Amine-Catalyzed Cascade Claisen−Schmidt and Iso-aromatization Reaction of **1**{*1*} and **2**{*1*}[a]



entry	catalyst	solvent (0.5 M)	temp (°C)	time (h)	yield (%)[b] **4**{*1,1*}	yield (%)[b] **5**{*1,1*}
1[c]	proline **3a**	DMSO	25	48	–	–
2[c]	proline **3a**	DMSO	75	24	–	–
3[d]	phenylalanine **3b**	DMSO	25	96	40	–
4[d]	**glycine 3c**	**DMSO**	**25**	**24**	**73**	**–**
5[c]	glycine **3c**	MeOH	75	12	8	–
6[d]	glycine **3c**	DMF	25	96	55	–
7	pyrrolidine **3d**/AcOH	DMF	25	12	–	30
8	pyrrolidine **3d**	DMF	25	6	–	65
9[c]	pyrrolidine **3d**	MeOH	25	24	–	–
10	**pyrrolidine 3d**	**DMF**	**25**	**12**	**–**	**75**
11[e]	**pyrrolidine 3d**	**DMF**	**25**	**12**	**–**	**77**
12[f]	pyrrolidine **3d**	DMF	25	2	60	5
13	pyrrolidine **3d**	DMF	60	2	–	61
14	pyrrolidine **3d**	DMSO	25	23	–	65
15	piperidine **3e**	DMF	25	12	–	61
16[c]	morpholine **3f**	DMF	25	12	–	–
17	benzylamine **3g**	DMF	25	24	30	–
18[c]	aniline **3h**	DMF	25	24	–	–
19[c]	DMAP **3i**	DMF	25	96	–	–
20[c]	triethylamine **3j**	DMF	25	12	–	–
21[c]	DBU **3k**	DMF	25	12	–	–
22	diamine **3l**	DMF	25	7	–	75
23	**diamine 3l**	**DMSO**	**25**	**7**	**–**	**80**
24	diamine **3l**	MeOH	25	24	10	10
25	diamine **3m**	DMF	25	8	–	62
26	diamine **3m**	DMSO	25	8	–	66

[a] Reactions were carried out in solvent (0.5 M) with the same proportions of Hagemann's ester **1**{*1*} and aldehyde **2**{*1*} in the presence of 20 mol % catalyst. [b] Yield refers to the column-purified product. [c] 70 to 85% of unreacted Hagemann's ester **1**{*1*} was isolated. [d] 1.25:1 Mixture of *E*/*Z* isomers were isolated. [e] 1.25 equivalents of ester **1**{*1*} was used. [f] 1:1 mixture of *E*/*Z* isomers were isolated.

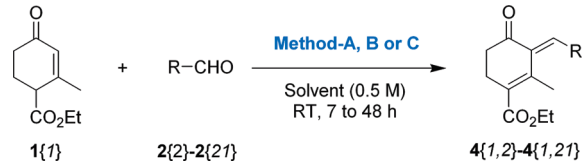
induced CS condensation looks like a strongly solvent-dependent reaction. The first step of the formation of the 1-amino-1,3-butadiene from the **1**{*1*} and amine **3d**, and its addition to the carbonyl (or imine) group, is facilitated in solvents of high polarity and the second step, 1,2-elimination, may be inhibited by protic solvents. Thus, dipolar aprotic solvents such as DMF and DMSO are especially useful for amine-catalyzed CS condensations.[7]

The structurally simple pyrrolidine **3d** catalyzed the cascade CS/IA reaction of **1**{*1*} and **2**{*1*} to produce **5**{*1,1*} in 65% yield at 25 °C for 6 h and extension of the reaction time to 12 h furnished the **5**{*1,1*} in 75% yield (Table 1, entries 8 and 10). Interestingly, the same reaction performed at 25 °C for 2 h furnished the **4**{*1,1*} in 60% yield with 1:1 mixture of *E*/*Z* isomers and **5**{*1,1*} in 5% yield (Table 1, entry 12). At 60 °C, the same reaction with pyrrolidine **3d** furnished the cascade CS/IA product **5**{*1,1*} in 61% yield in reduced time (Table 1, entry 13). Piperidine **3e** also catalyzed the cascade CS/IA reaction in 61% yield, but there is no reaction under morpholine **3f**-catalysis (Table 1, entries 15 and 16). Primary amines like benzylamine **3g** catalyzed the CS reaction of **1**{*1*} and **2**{*1*} to furnish **4**{*1,1*} in 30% yield, but there is no reaction under aniline **3h**-catalysis (Table 1, entries 17 and 18). The *tert*-amines like DMAP **3i**, triethylamine **3j**, and DBU **3k** did not catalyze the cascade CS or CS/IA reaction, which is giving strong evidence for the in situ enamine formation during these reactions.

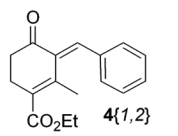
After successful demonstration of glycine- and pyrrolidine-catalyzed cascade CS and CS/IA reactions, we further screened diamine-based catalysts to increase the reaction yield and regioselectivity of the cascade reaction of **1**{*1*} and **2**{*1*}. The (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** catalyzed the cascade CS/IA reaction of **1**{*1*} and **2**{*1*} at 25 °C for 7 h in DMF to produce **5**{*1,1*} in 75% yield (Table 1, entry 22). Interestingly, the same reaction in DMSO at 25 °C for 7 h furnished the cascade CS/IA product **5**{*1,1*} in 80% yield, which is better-optimized condition compared to glycine- and pyrrolidine-catalysis (Table 1, entry 23). Surprisingly, cascade CS/IA reaction of **1**{*1*} and **2**{*1*} under (*S*)-1-(pyrrolidin-2-ylmethyl)piperidine **3m**-catalysis in DMF or DMSO at 25 °C for 8 h furnished the product **5**{*1,1*} in 62−66% yield, which is not superior compared to **3l**-catalysis (Table 1, entries 25 and 26). The optimal reaction conditions for push−pull olefin synthesis involved glycine **3c**-catalysis at 25 °C in DMSO with equimolar quantities of **1**{*1*} and **2**{*1*}, which furnished the CS product **4**{*1,1*} in 73% yield (Table 1, entry 4). The optimal reaction conditions for push−pull phenol synthesis involved pyrrolidine **3d-** or diamine **3l**-catalysis at 25 °C in DMF or DMSO with equimolar quantities of **1**{*1*} and **2**{*1*}, which furnished the cascade CS/IA product **5**{*1,1*} in 75 or 80% yield respectively (Table 1, entries 10 and 23). The regiochemistry of products **4**{*1,1*} and **5**{*1,1*} was established by NMR analysis.

Diversity-Oriented Synthesis of Push−Pull Olefins 4{*1,2*}−4{*1,21*} and Functionalized Aldehydes 6{*1,19*}/6{*1,20*} via Amine-Catalysis. With an efficient amino acid- or amine-catalyzed CS and CS/IA protocol in hand, the scope of the glycine-catalyzed CS and pyrrolidine- or diamine-catalyzed CS/IA reactions was investigated with various aldehydes **2**{*2*}-**2**{*21*} by monitoring the electronic nature of aldehydes **2** or/and basic nature of catalyst **3** in cascade CS and CS/IA reactions. A series of neutral, electron-donating, electron-withdrawing and α,β-unsaturated aldehydes **2**{*2*}-**2**{*21*} were reacted with 1.0 equiv of Hagemann's ester **1**{*1*} catalyzed by 20 mol % of glycine **3c**, pyrrolidine **3d**, or diamine **3l** at 25 °C for 7−48 h in DMSO or DMF (Table 2). Interestingly, iso-aromatization did not taken place in all these reactions and only the CS products, 3-arylidene Hagemann's esters **4**{*1,2*}-**4**{*1,21*} were isolated in moderate to good yields with stereoselectivities favoring the *E*-isomers except in the case of α,β-unsaturated aldehydes **2**{*19*}-**2**{*21*}.

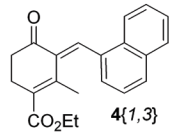
Table 2. Synthesis of Chemically Diverse Libraries of 3-Arylidene-Hagemann's Esters **4** via Amine-Catalysis[a]



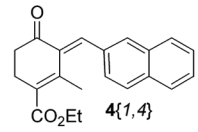
1{*1*} **2**{*2*}-**2**{*21*} **4**{*1,2*}-**4**{*1,21*}



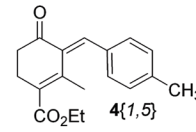
M-A: 80% (*E*/*Z* = 3.5:1)
M-B: 55% (*E*/*Z* = 5.3:1)
M-C: 45% (*E*/*Z* = 3.8:1)



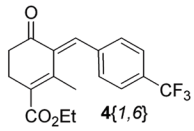
M-B: 55% (*E*/*Z* = 4.0:1)



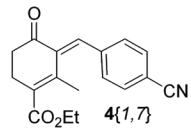
M-B: 50% (*E*/*Z* = 3.0:1)



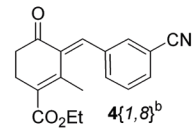
M-A: 70% (*E*/*Z* = 3.5:1)
M-B: 35% (*E*/*Z* = 5.5:1)



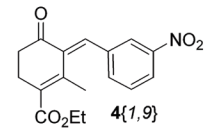
M-A: 81% (*E*/*Z* = 2.0:1)



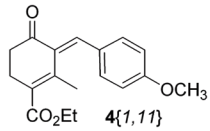
M-A: 71% (*E*/*Z* = 2.0:1)
M-B: 85% (*E*/*Z* = 1.5:1)



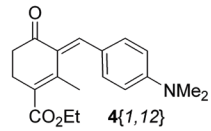
M-A: 55% (*E*/*Z* = 10:1)



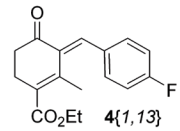
M-A: 55% (*E*/*Z* = 1.5:1)



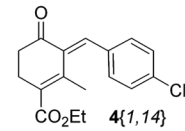
M-A: 55% (*E*/*Z* = 3.3:1)
M-B: 25% (*E*/*Z* = 3.5:1)



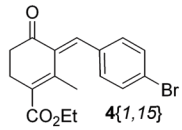
M-C: 50% (*E*/*Z* = 99:1)



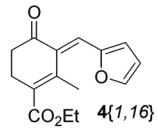
M-A: 70% (*E*/*Z* = 5.0:1)
M-B: 60% (*E*/*Z* = 3.5:1)
M-C: 50% (*E*/*Z* = 2.3:1)



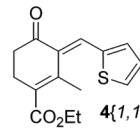
M-B: 50% (*E*/*Z* = 3.8:1)
M-C: 55% (*E*/*Z* = 2.0:1)



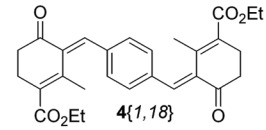
M-A: 62% (*E*/*Z* = 3.0:1)
M-B: 35% (*E*/*Z* = 3.5:1)



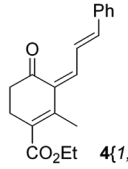
M-A: 81% (*E*/*Z* = 6.0:1)
M-B: 45% (*E*/*Z* = 99:1)



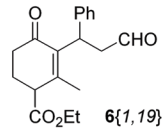
M-A: 62% (*E*/*Z* = 2.0:1)
M-B: 45% (*E*/*Z* = 99:1)



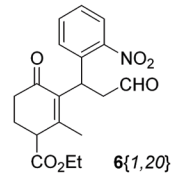
M-C: 75% (*E*/*Z* = 99:1)



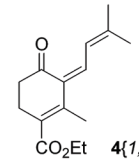
M-A: 50% (*E*/*Z* = 1:8)
M-C: 75% (*E*/*Z* = 1:6)



M-B: 65% (*dr* = 1:1)



M-B: 65% (*dr* = 1.2:1)



M-C: 60% (*E*/*Z* = 1:5)

[a] **Method-A:** Reactions were carried out in DMSO (0.5 M) with the same proportions of Hagemann's ester **1**{*1*} and aldehyde **2** in the presence of 20 mol % glycine **3c**.; **Method-B:** Reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **1**{*1*} and aldehyde **2** in the presence of 20 mol % pyrrolidine **3d**.; **Method-C:** Reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **1**{*1*} and aldehyde **2** in the presence of 20 mol % diamine **3l**. Yield refers to the column-purified product and *E*/*Z* ratio determined by NMR analysis. [b] Hagemann's ester **1**{*1*} (1.0 mmol) reacted with aldehyde **2**{*8*} (0.5 mmol) in the presence of 20 mol % glycine **3c** at 65 °C for 12 h. [c] Hagemann's ester **1**{*1*} (1.0 mmol) reacted with aldehyde **2**{*21*} (0.5 mmol) in the presence of 20 mol % diamine **3l** at 0 °C in DMF for 0.5 h.

The ethyl (*E*)-3-benzylidene-2-methyl-4-oxo-cyclohex-1-enecarboxylate **4**{*1,2*} were obtained as major isomer with excellent to good yields via **3c**-, **3d**-, or **3l**-catalyzed CS reaction of **1**{*1*} with **2**{*2*} at 25 °C in DMSO or DMF, respectively (Table 2, entry 1). Unfortunately, the same CS reaction of **1**{*1*} with **2**{*2*} under **3c**-, **3d**-, or **3l**-catalysis at 70−75 °C in DMSO or DMF furnished the CS product **4**{*1,2*} in only 25−30% yields, and this may be due to the decomposition of **2**{*2*} at higher temperatures (results not shown in Table 2). The CS reaction of **1**{*1*} with benzaldehydes containing an electron-withdrawing group **2**{*6*}-**2**{*9*} also under glycine **3c**-catalysis furnished the CS products (*E*)-**4**{*1,6*}-**4**{*1,9*} as major isomers with 10:1 to 1.5:1 *E*/*Z* ratio with good yields (Table 2, entries 5−8). Interestingly, halogenated benzaldehydes **2**{*13*}-**2**{*15*} and heterocyclic aldehydes **2**{*16*}-**2**{*17*} also furnished the expected CS products **4**{*1,13*}-**4**{*1,17*} with **1**{*1*} under **3c**-catalysis in good yields with *E*-isomer as major (Table 2, entries 11−15). Reaction of **1**{*1*} with *trans*-cinnamaldehyde **2**{*19*} under glycine **3c** catalysis furnished the CS product **4**{*1,19*} in 50% yield with a 1:8 *E*/*Z* ratio (Table 2, entry 17).

Compared to glycine-catalysis, pyrrolidine-catalysis generated the CS products **4**{*1,2*}-**4**{*1,17*} with less yields and

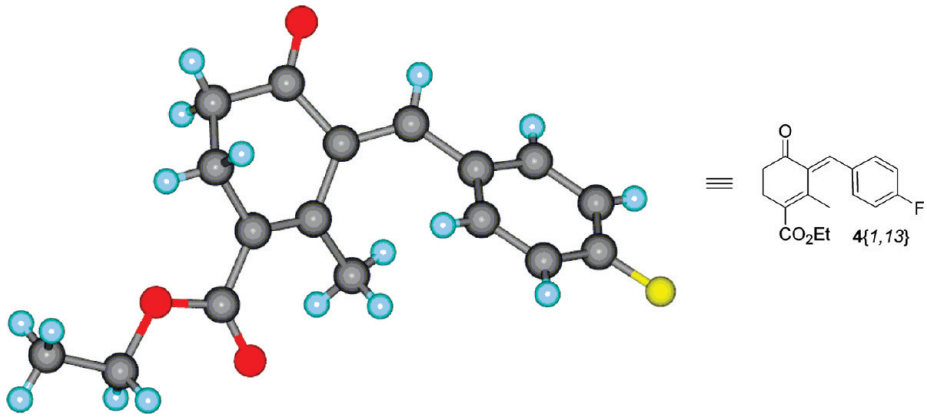


Figure 3. Crystal structure of ethyl 3-(4-fluorobenzylidene)-2-methyl-4-oxo-cyclohex-1-enecarboxylate (**4**{*1,13*}).

high *E*-selectivity from **1**{*1*} and benzaldehydes **2**{*2*}-**2**{*17*} at 25 °C for 12−24 h in DMF as shown in Table 2. Observation of high *E*-selectivity in pyrrolidine-catalysis may be due to the steric hindrance induced by **3d** in the transition state of CS reactions (for clear discussion, see in the mechanistic insights). Reaction of **1**{*1*} with *trans*-cinnamaldehyde **2**{*19*} under pyrrolidine **3d** catalysis furnished the Michael product **6**{*1,19*} in 65% yield in a 1:1 diastereomeric ratio, which is different from the glycine-catalysis maybe because of the nature of **2**{*19*} as Michael acceptor under pyrrolidine-catalysis (Table 2, entry 18). Formation of Michael adducts **6** from **1**{*1*} and α,*β*-unsaturated aldehyde under pyrrolidine-catalysis is confirmed by one more example as shown in Table 2, entry 19.

A series of neutral, electron-donating and α,*β*-unsaturated aldehydes **2** were reacted with 1.0 equiv of Hagemann's ester **1**{*1*} catalyzed by 20 mol % of diamine **3l** at 25 °C for 7−18 h in DMF or DMSO solvents (Table 2). Interestingly, in these reactions also CS/IA products **5** are not furnished, and only the CS products, 3-arylidene Hagemann's esters **4** were isolated in moderate to good yields with stereoselectivities favoring the *E*-isomers for simple benzaldehydes and favoring the *Z*-isomers for α,*β*-unsaturated aldehydes without formation of Michael adducts **6** (Table 2).

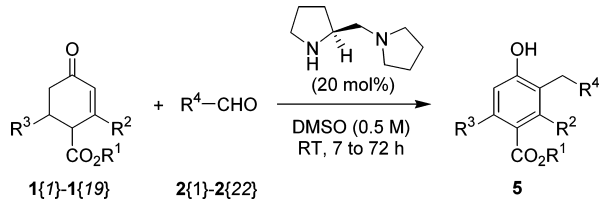
Interestingly, 4-(dimethylamino)benzaldehyde **2**{*12*} and benzene-1,4-dicarbaldehyde **2**{*18*} furnished the only CS products **4**{*1,12*} and **4**{*1,18*} with **1**{*1*} under **3l**-catalysis in good yields with high *E*-selectivity as shown in Table 2. Interestingly, reaction of **1**{*1*} with *trans*-cinnamaldehyde **2**{*19*} under diamine **3c**-catalysis furnished the CS product (*E*, *Z*, *E*)-triene **4**{*1,19*} in 75% yield with 1:6 *E*/*Z* ratio, which is different from the pyrrolidine-catalysis but similar to the glycine-catalysis. Formation of CS product, (*E*, *Z*, *E*)-triene from **1**{*1*} and α,*β*-unsaturated aldehyde under diamine-catalysis is confirmed by one more example as shown in Table 2. Reaction of 2.0 equiv of **1**{*1*} with 3,3-dimethylacrolein **2**{*21*} in DMF at 0 °C for 0.5 h under **3l**-catalysis furnished the selective conjugated (*E*, *Z*, *E*)-triene **4**{*1,21*} in 60% yield with 1:5 *E*/*Z* ratio (Table 2, entry 20). Structure and regiochemistry of CS products **4** were confirmed by NMR and mass analysis and also finally confirmed by X-ray structure analysis on **4**{*1,13*} as shown in Figure 3.[8]

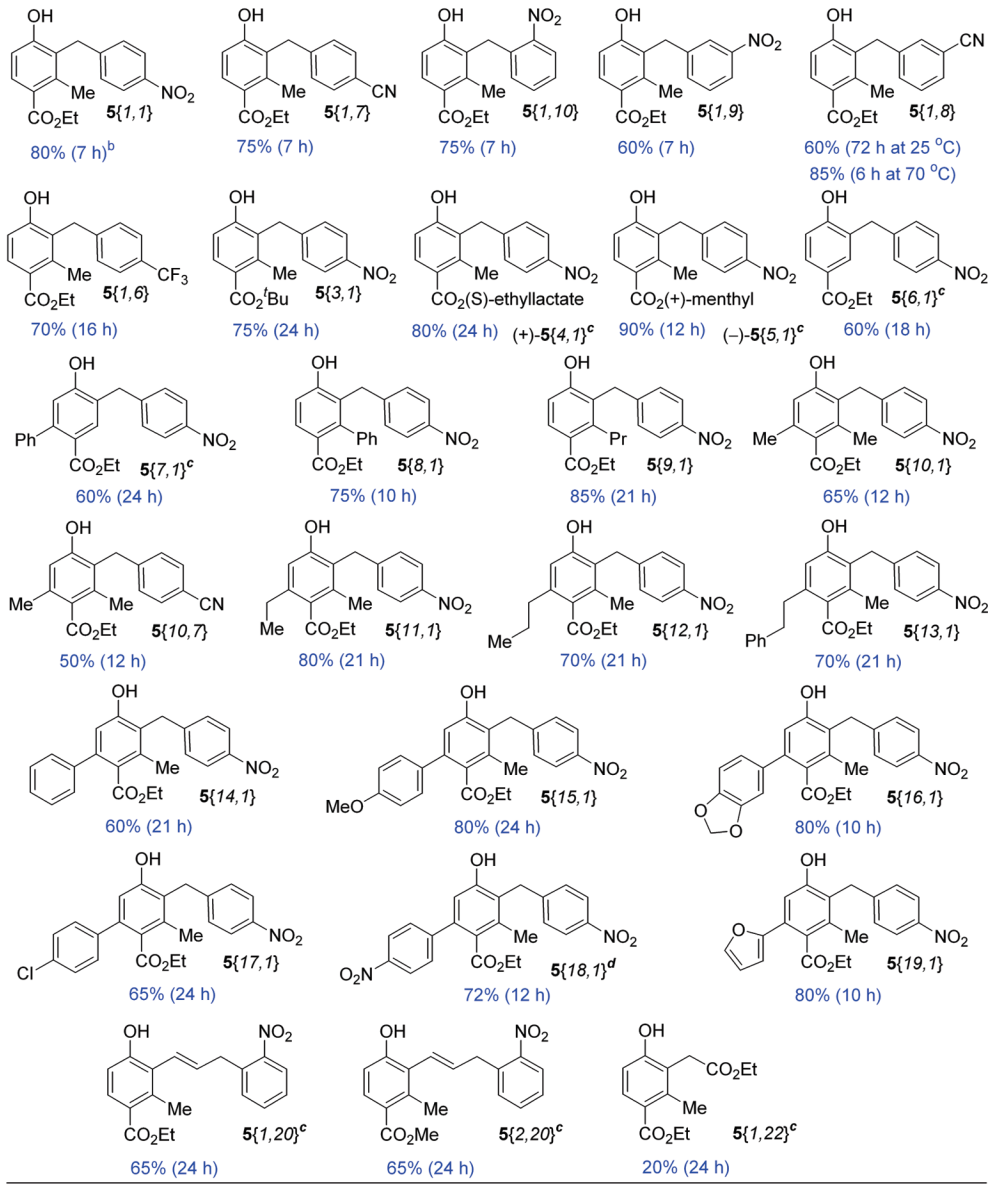
The results in Table 2 demonstrate the broad scope of this novel CS methodology covering a structurally diverse group of aldehydes **2** with good yields and selectivity. 2-Arylidenecyclohexanones, 2,6-bis(arylidene)cyclohexanones and related compounds were evaluated for antitumor, anti-inflammatory, antineoplastic, cytotoxic activity, and also for the inhibition of mitochondrial function in yeast emphasizing the value of this amino-acid catalyzed CS approach.[4a−e] In addition, generation of molecular diversity around the 2-arylidenecyclohexanone scaffolds may allow for the identification of more potent species.

Diversity-Oriented Synthesis of Push−Pull Phenols 5 via Diamine-Catalysis. After thorough investigation of the glycine **3c**-, pyrrolidine **3d**- and diamine **3l**-catalyzed CS reactions of Hagemann's ester **1**{*1*} with various aldehydes **2**{*1*}-**2**{*21*} [Tables 1 and 2], we further screened only benzaldehydes **2** containing an electron-withdrawing group with variety of Hagemann's esters **1**{*1*}-**1**{*19*} under diamine **3l**-catalysis to look at the high-yielding formation of CS/IA products **5** (Table 3). A series of benzaldehydes **2** containing an electron-withdrawing group and α,*β*-unsaturation were reacted with 1.0 equiv of Hagemann's esters **1**{*1*}-**1**{*19*} catalyzed by 20 mol % of (*S*)-diamine **3l** at 25 °C for 7−72 h in DMSO. Interestingly, in all these reactions expected CS/IA products or push−pull phenols **5** were furnished with moderate to very good yields as shown in Table 3.

Functionalized push−pull phenols **5** are an important class of compounds, which are widely used as intermediates in the pharmaceuticals.[4f−l] Compounds containing 2-alkyl-push−pull phenols **5** have found pharmaceutical applications as remedies for diabetes **G**, insulin resistance **H**, antiasthmatic LTD4 antagonist ICI-204/219 **I**, lasiodiplodin analogues **J**, and also starting materials for the synthesis of natural products as shown in Chart 1.[4f−l] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[6] L-Diamine-catalyzed cascade CS/IA reaction of **1**{*1*} with 4-cyanobenzaldehyde **2**{*7*} in DMSO at 25 °C for 7 h furnished the expected product **5**{*1,7*} in 75% yield (Table 3, entry 2). The CS/IA reaction of 2-nitro- and 3-nitrobenzaldehydes **2**{*10*}/**2**{*9*} with **1**{*1*} catalyzed by L-**3l** in DMSO at 25 °C for 7 h furnished the expected **5**{*1,10*}/**5**{*1,9*} with 75−60% yields respectively as shown in Table 3. After these interesting results, we decided to investigate the scope and limitations of the CS/IA reaction with other two aldehydes containing an electron withdrawing group **2**{*6*}/**2**{*8*} with **1**{*1*} under L-diamine-catalysis at the ambient conditions

Table 3. Synthesis of Chemically Diverse Libraries of Highly Substituted Phenols **5** via Diamine-Catalysis[a]





[a] All reactions were carried out in DMSO (0.5 M) with the same proportions of Hagemann's ester **1** and aldehyde **2** in the presence of 20 mol % diamine **3 L.** [b] Yield refers to the column-purified product. [c] Hagemann's ester **1** (1.0 mmol) reacted with aldehyde **2**{*1*} (0.5 mmol) in the presence of 20 mol % diamine **3l** at 25 °C for 12−24 h. [d] Hagemann's ester **1**{*18*} (1.0 mmol) reacted with aldehyde **2**{*1*} (0.5 mmol) in the presence of 20 mol % diamine **3l** at 70 °C for 12 h.

(Table 3, entries 5−6). Interestingly, CS/IA reaction of 3-cyanobenzaldehyde **2**{*8*} and 4-trifluoromethyl-benzaldehyde **2**{*6*} with **1**{*1*} under L-diamine-catalysis at 25 °C for 72−16 h furnished the expected push−pull phenols **5**{*1,8*} and **5**{*1,6*} in 60/70% yields respectively as shown in Table 3, entries 5−6. Yield of cascade CS/IA product **5**{*1,8*} was increased to 85% when reaction was performed at 70 °C for 6 h as shown in Table 3, entry 5.

After these interesting results, we further decided to investigate the scope and limitations of the CS/IA reaction with a range of Hagemann's esters **1**{*1*}-**1**{*19*} including chiral Hagemann's esters **1**{*4*}-**1**{*5*}, simple ester **1**{*6*}, and 6-substituted Hagemann's esters **1**{*7*}-**1**{*19*} with 4-nitrobenzaldehyde **2**{*1*}, 4-cyanobenzaldehyde **2**{*7*}, 3-(2-nitrophenyl)propenal **2**{*20*}, and ethyl glyoxylate **2**{*22*} under L-diamine-catalysis in DMSO at the ambient conditions

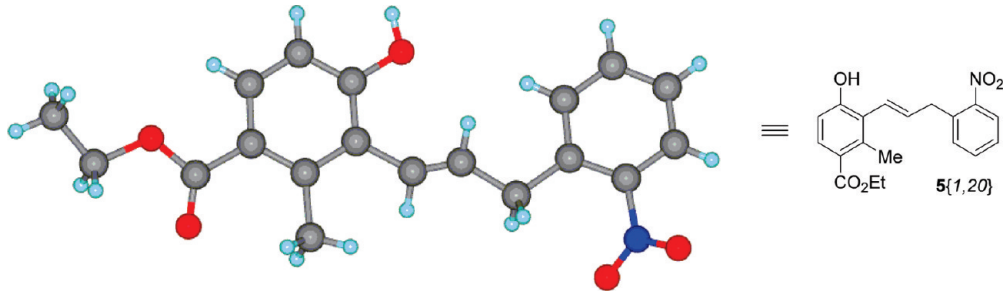
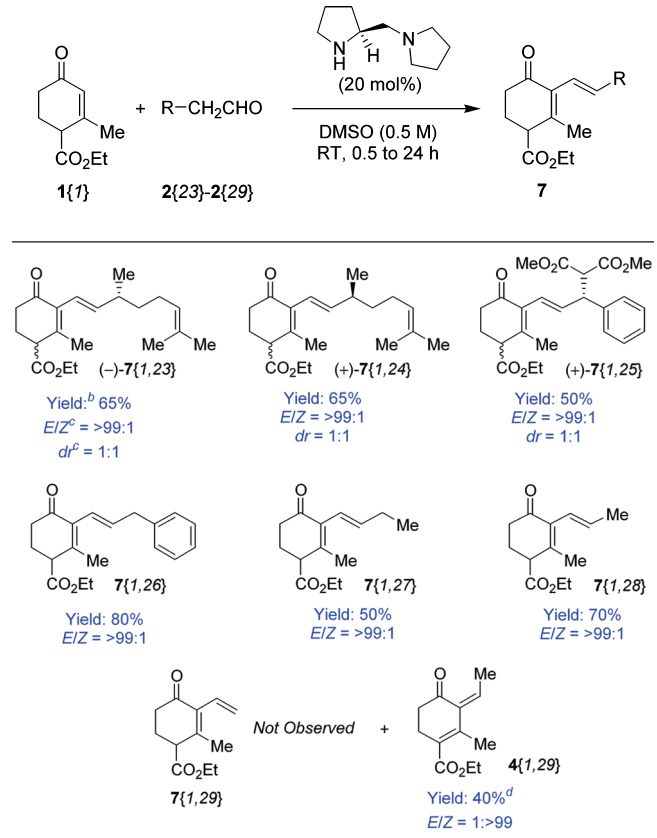


Figure 4. Crystal structure of ethyl 4-hydroxy-2-methyl-3-[3-(2-nitrophenyl)propenyl]-benzoate (**5**{*1,20*}).

to test the diversity nature of the CS/IA reaction (Table 3). As shown in Table 3, CS/IA reaction of *t*-butyl ester **1**{*3*} with **2**{*1*} under **3l**-catalysis for 24 h furnished the phenol **5**{*3,1*} with 75% yield (Table 3, entry 7). Interestingly, CS/IA reaction of 4-nitrobenzaldehyde **2**{*1*} with 2.0 equiv of chiral Hagemann's esters **1**{*4*}-**1**{*5*} under **3l**-catalysis in DMSO at 25 °C for 24−12 h furnished the chiral push−pull phenols (+)-**5**{*4,1*} in 80% yield and (−)-**5**{*5,1*} in 90% yield as shown in Table 3, entries 8/9. Diamine-catalyzed CS/IA reaction of 4-nitrobenzaldehyde **2**{*1*} with simple Hagemann's esters **1**{*6*}-**1**{*9*} in DMSO at 25 °C for 10−24 h furnished the expected push−pull phenols **5**{*6,1*}-**5**{*9,1*} in 60−85% yields respectively as shown in Table 3, entries 10−13. Interestingly, CS/IA reaction of 4-nitrobenzaldehyde **2**{*1*} with 6-methyl-Hagemann's ester **1**{*10*} under **3l**-catalysis in DMSO at 25 °C for 12 h furnished the highly functionalized push−pull phenol **5**{*10,1*} in 65% yield as shown in Table 3, entry 14. Generality of the diamine-catalyzed CS/IA reaction of 6-substituted Hagemann's esters **1** with 4-nitrobenzaldehyde **2**{*1*} or 4-cyanobenzaldehyde **2**{*7*} were confirmed by 10 more examples with esters **1**{*10*}-**1**{*19*} containing different functional groups under **3l**-catalysis and furnished the expected highly substituted push−pull phenols **5**{*10,1*}-**5**{*19,1*} with 50−80% yields respectively as shown in Table 3.

Interestingly, cascade reaction of 3-(2-nitrophenyl)propenal **2**{*20*} and ethyl glyoxylate **2**{*22*} with **1**{*1*} under L-diamine-catalysis furnished the novel products **5**{*1,20*} in 65% yield via CS/IA/I and **5**{*1,22*} in 20% yield via CS/IA reactions as shown in Table 3, entries 25−27. Generality of the **3l**-catalyzed cascade CS/IA/I reaction was confirmed by one more example with **1**{*2*} and **2**{*20*} as shown in Table 3. Structure and regiochemistry of CS/IA/I products **5**{*1,20*}/**5**{*2,20*} were confirmed by NMR and mass analysis and also finally confirmed by X-ray structure analysis on **5**{*1,20*} as shown in Figure 4.[8] Presently developed amine-catalyzed CS/IA/I reaction looks as novel technology for the *ortho*-vinylation of in situ generated functionalized phenols compared to metal mediated *ortho*-vinylation of preformed phenols.[9] Functionalized push−pull phenols **5** are useful intermediates for the synthesis of analogues of remedies for diabetes **G**, insulin resistance **H**, antiasthmatic LTD4 antagonist ICI-204/219 **I**, lasiodiplodin analogues **J**, and also for the synthesis of natural products as shown in Chart 1.[4f−l] This CS/IA technology may be suitable to develop a large number of diverse-compounds of **5** to screen and identify the suitable bioactive products.

Table 4. Synthesis of Chemically Diverse Libraries of 1,3-Dienes **7** via Diamine-Catalysis[a]



[a] Hagemann's ester **1**{*1*} (1.0 mmol) reacted with aldehyde **2**{23}-**2**{*29*} (0.5 mmol) in the presence of 20 mol % diamine **3l** at 25 °C in DMSO for 0.5 to 24 h. [b] Yield refers to the column-purified product. [c] *E/Z* and *dr* ratio determined by NMR analysis. [d] Reaction stirred at 0 °C in DMF for 0.5 h.

Diversity-Oriented Synthesis of Highly Functionalized (*E*)-1,3-Dienes 7 via Diamine-Catalysis. After thorough investigation of the diamine **3l**-catalyzed CS, CS/IA, and CS/IA/I reactions of Hagemann's esters **1** with various aldehydes **2**, we further showed interest to screen aliphatic aldehydes **2**{*23*}-**2**{*29*} containing an α-hydrogen with Hagemann's ester **1**{*1*} under diamine **3l**-catalysis to look at the effect of electronic factors of substrates on product formation (Table 4). A series of aliphatic aldehydes **2**{*23*}-**2**{*29*} containing an α-hydrogen were reacted with 2.0 equiv of Hagemann's ester **1**{*1*} catalyzed by 20 mol % of (*S*)-diamine **3l** at 25 °C for 0.5−24 h in DMSO (0.5 M). Surprisingly, in all these reactions unexpected CS/I products **7** were furnished in moderate to very good yields with high selectivity instead of CS products **4** as shown in Table 4.

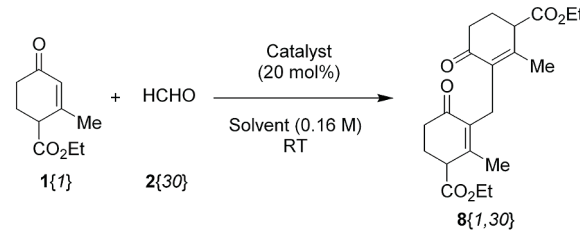
Interestingly, cascade reaction of optically pure (*R*)-(+)-citronellal **2**{*23*} with 2.0 equiv of Hagemann's ester **1**{*1*} under **3l**-catalysis in DMSO at 25 °C for 24 h furnished the chiral functionalized (*E*)-1,3-diene (−)-**7**{*1,23*} in 65% yield with >99:1 ratio of *E*:*Z* isomers and 1:1 ratio of diastereomers as shown in Table 4, entry 1. Unexpected formation of product (−)-**7**{*1,23*} from **1**{*1*} and **2**{*23*} via **3l**-catalysis can be explained through cascade Claisen−Schmidt/isomerization (CS/I) reactions, and further reaction mechanism is discussed in the mechanistic insights. Diamine-catalyzed CS/I reaction of optically pure opposite enantiomer (*S*)-(−)-citronellal **2**{*24*} with simple Hagemann's ester **1**{*1*} in DMSO at 25 °C for 24 h furnished the chiral functionalized (*E*)-1,3-diene (+)-**7**{*1,24*} in 65% yield with >99:1 ratio of *E*:*Z* isomers and 1:1 ratio of diastereomers as shown in Table 4, entry 2. The generality of the diamine-catalyzed CS/I reaction of Hagemann's ester **1**{*1*} with chiral aliphatic aldehyde was confirmed by one more example with dimethyl 2-(3-oxo-1-phenylpropyl)malonate [93% ee, (−)-**2**{*25*}] containing an α-hydrogen under **3l**-catalysis, which furnished the expected highly substituted chiral (*E*)-1,3-diene (+)-**7**{*1,25*} in 50% yield with >99:1 ratio of *E*:*Z* isomers and 1:1 ratio of diastereomers as shown in Table 4, entry 3.

After successful demonstration of diamine-catalyzed cascade CS/I reaction of **1**{*1*} with chiral aldehydes **2**{*23*}-**2**{*25*}, we further investigated the scope and limitations of the cascade CS/I reaction with a range of achiral aliphatic aldehydes **2**{*26*}-**2**{*29*} containing an α-hydrogen under L-diamine-catalysis in DMSO at the ambient conditions to test the diversity nature of the CS/I reaction (Table 4). Cascade CS/I reaction of ester **1**{*1*} with 3-phenylpropionaldehyde **2**{*26*} under **3l**-catalysis for 17 h furnished the achiral (*E*)-1,3-diene **7**{*1,26*} in 80% yield with >99:1 ratio of *E*:*Z* isomers as shown in Table 4, entry 4. In a similar manner, cascade CS/I reaction of butyraldehyde **2**{*27*} and propionaldehyde **2**{*28*} with 2.0 equiv of Hagemann's ester **1**{*1*} under **3l**-catalysis in DMSO at 25 °C for 24/12 h furnished the achiral (*E*)-1,3-dienes **7**{*1,27*} in 50% yield with >99:1 ratio of *E*:*Z* isomers and **7**{*1,28*} in 70% yield with >99:1 ratio of *E*:*Z* isomers, respectively as shown in Table 4, entries 5/6. Interestingly, cascade CS/I reaction of Hagemann's ester **1**{*1*} with acetaldehyde **2**{*29*} under **3l**-catalysis in DMSO is not a clean reaction, but the same reaction in DMF at 0 °C for 0.5 h furnished the only CS product **4**{*1,29*} in 40% yield with 1:>99 ratio of *E*:*Z* isomers instead of expected 1,3-diene **7**{*1,29*} as shown in Table 4, entry 7.

Amine-induced cascade CS/I reaction is first time to observe, and certainly this CS/I technology is suitable to develop a large number of diverse-compounds of **7** to screen and identify the suitable intermediates for the bioactive and natural product synthesis.

Diversity-Oriented Synthesis of Highly Functionalized bis-Enones 8 via Piperidine-Catalysis. After the investigation of the amino acid- or amine **3**-catalyzed CS, CS/IA, CS/IA/I, and CS/I reactions of Hagemann's esters **1**{*1*}-**1**{*19*} with various aldehydes **2**{*1*}-**2**{*29*}, we were further interested to screen simple formaldehyde **2**{*30*} with Hagemann's ester **1**{*1*} under amine **3**-catalysis (Tables 5 and 6). Interestingly, reaction of 37% aqueous formaldehyde **2**{*30*} with 2.0 equiv of Hagemann's ester **1**{*1*} under proline **3a**-catalysis in DMSO at 25 °C for 24 h furnished the functionalized *bis*-enone **8**{*1,30*} in 55% yield with >99% de as shown in Table 5, entry 1. Unexpected formation of product **8**{*1,30*} from **1**{*1*} and **2**{*30*} via **3a**-catalysis can be explained through cascade Claisen−Schmidt/Michael (CS/M) reactions and further information on the reaction mechanism is discussed in the mechanistic insights. Diversity-oriented high-yielding one-pot synthesis of **8** through amine-catalysis is very much needed because functionalized *bis*-

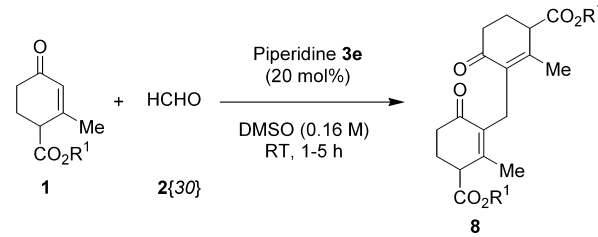
Table 5. Optimization of the Direct Amine-Catalyzed Cascade Claisen−Schmidt and Michael reaction of **1**{*1*} and **2**{*30*}[a]

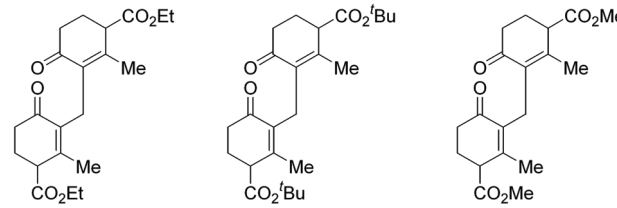


entry	catalyst (20 mol%)	solvent (0.16 M)	time (h)	yield (%)[b] **8**{*1,30*}
1	proline **3a**	DMSO	24	55
2	glycine **3c**	DMSO	24	55
3[c]	pyrrolidine **3d**	DMSO	4	65
4	**pyrrolidine 3d**	**DMSO**	**1**	**76**
5	pyrrolidine **3d**	DMF	1	70
6	**piperidine 3e**	**DMSO**	**1**	**80**
7	diamine **3l**	DMSO	1	72

[a] Reactions were carried out in solvent (0.16 M) with the 2.0 equiv of Hagemann's ester **1**{*1*} to 37% aqueous formaldehyde **2**{*30*} in the presence of 20 mol % catalyst. [b] Yield refers to the column-purified product. [c] 1:1 ratio of ester **1**{*1*} and 37% aqueous formaldehyde **2**{*30*} was used.

Table 6. Synthesis of Dienones **8** via Direct Amine-Catalyzed Cascade Claisen−Schmidt/Michael Reactions[a,b]





[a] See Experimental Section. [b] Yield refers to the column purified product.

enones **8** would be suitable intermediates for the synthesis of terpenoid natural products.[10]

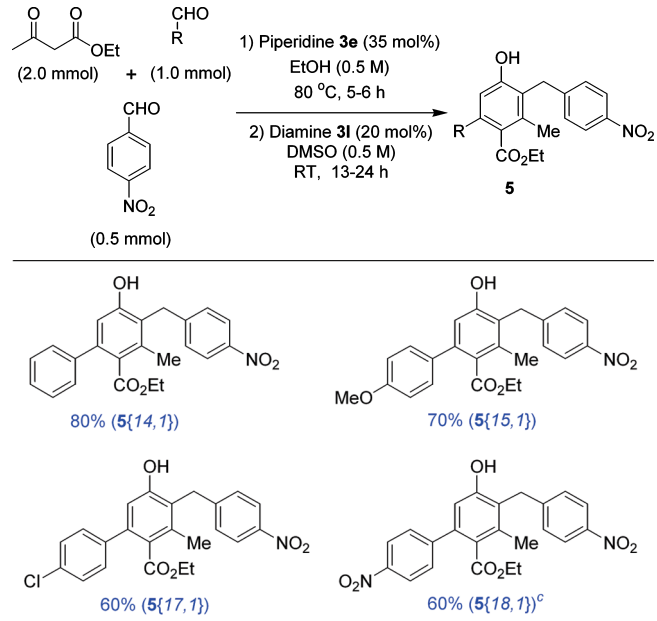
For the high-yielding one-pot synthesis of *bis*-enone **8**{*1,30*} from simple substrates **1**{*1*} and **2**{*30*}, we further screened catalyst and solvent effect on the cascade CS/M reaction as shown in Table 5. The cascade CS/M reaction of **1**{*1*} and **2**{*30*} under glycine **3c**-catalysis is similar to **3a**-catalysis, but the same reaction under pyrrolidine **3d**-catalysis furnished the product **8**{*1,30*} with improved yield (76%) as shown in Table 5, entries 2−4. DMSO looks like a better solvent for cascade CS/M reaction of **1**{*1*} and **2**{*30*} compared to DMF under **3d**-catalysis (Table 5, entry 5). The CS/M reaction yield is increased to 80% under the piperidine **3e**-catalysis in DMSO for 1 h at 25 °C as shown in Table 5, entry 6. Diamine-catalyzed CS/M reaction of **2**{*30*} with **1**{*1*} in DMSO at 25 °C for 1 h furnished the functionalized *bis*-enone **8**{*1,30*} in 72% yield with >99% de, which is not superior compared to piperidine-catalysis as shown in Table 5, entry 7. The optimized reaction conditions for *bis*-enone synthesis involved piperidine **3e**-catalysis at 25 °C in DMSO with 2 equiv of **1**{*1*} and **2**{*30*}, which furnished the cascade product **8**{*1,30*} in 80% yield with >99% de (Table 5, entry 6).

Generality of the piperidine-catalyzed CS/M reaction of formaldehyde **2**{*30*} with Hagemann's esters **1** was confirmed by two more examples with *t*-butyl ester **1**{*3*} and methyl ester **1**{*2*} under **3e**-catalysis, which furnished the expected highly substituted *bis*-enones **8**{*3,30*} in 20% yield with >99% de and **8**{*2,30*} in 60% yield with >99% de as shown in Table 6.

Applications of the Push−Pull Dienamine Chemistry. A. Development of Sequential One-Pot Combination of Cascade Reactions Based on the CS/IA Platform. Functionalized phenols **5** are an important class of compounds, which are widely used as intermediates in the pharmaceuticals and natural product synthesis as shown in Chart 1.[4] As such, the development of new and more general one-pot catalytic methods for their high-yielding preparation is of significant interest.[6] Hagemann's esters **1**{*1*}-**1**{*19*} were synthesized in good yields with minor modifications of known methods of direct piperidine- or KO^{t}Bu-catalyzed cascade Knoevenagel/Michael/aldol condensation/decarboxylation (K/M/A/DC) reactions of alkyl acetoacetates and aldehydes (Table 7).[7b] Herein, we utilized the direct sequential combination of piperidine-catalyzed cascade K/M/A/DC and diamine-catalyzed cascade CS/IA of ethyl acetoacetate, aldehydes and 4-nitrobenzaldehyde to furnish the functionalized phenols **5** with high yields in one-pot (Table 7).

Cascade K/M/A/DC reaction of 2 equiv of ethyl acetoacetate and benzaldehyde **2**{*2*} under piperidine-catalysis in EtOH at 80 °C for 5−6 h furnished the expected Hagemann's ester **1**{*14*} with >99% conversion, which on in situ treatment with 4-nitrobenzaldehyde **2**{*1*} at 25 °C in the same solvent did not furnished the expected product **5**{*14,1*} in good yield; but removing the solvent EtOH by vacuum pump and adding solvent DMSO, 20 mol % of diamine **3l** and 4-nitrobenzaldehyde **2**{*1*} to the reaction mixture of cascade K/M/A/DC furnished the expected product **5**{*14,1*} in 80% yield as shown in Table 7, entry 1. Successful sequential one-pot combination of two cascade K/M/A/DC and CS/IA reactions under piperidine-/diamine-catalysis was demonstrated by three more examples with good yields as shown in Table 7, and this one-pot synthetic strategy will show much impact on the synthesis of functionalized phenols **5** from simple substrates.

Table 7. Sequential Combination of Cascade Knoevenagel/Michael/Aldol Condensation/Decarboxylation and Cascade Claisen−Schmidt/Iso-Aromatization Reactions in One-Pot[a,b]

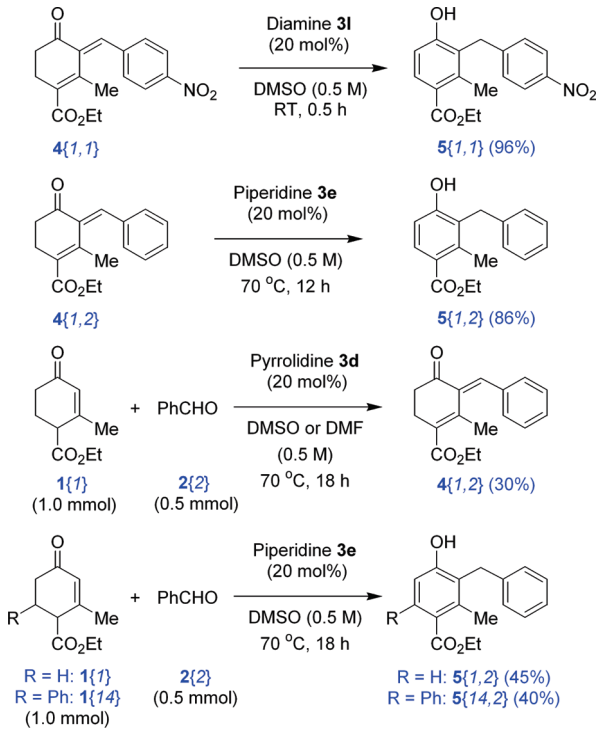


[a] See Experimental Section. [b] Yield refers to the column purified product. [c] Second reaction performed at 70 °C for 14 h.

B. Base-Catalyzed Iso-Aromatization of CS Products. After successful synthesis of functionalized push−pull phenols **5** from Hagemann's esters **1** and benzaldehydes **2** containing an electron-withdrawing group under diamine-catalysis, we thought of testing how much the basic nature of amine **3** and electronic nature of substrates **1/2** will control the iso-aromatization of CS products **4** as shown in Scheme 2. Interestingly, treatment of pure CS product **4**{*1,1*} with 20 mol % of diamine **3l** in DMSO at 25 °C for 0.5 h furnished the phenol **5**{*1,1*} in 96% yield via iso-aromatization as shown in Scheme 2. In a similar manner, treatment of pure CS product **4**{*1,2*} with 20 mol % of piperidine **3e** in DMSO at 70 °C for 12 h furnished the phenol **5**{*1,2*} in 86% yield via iso-aromatization as shown in Scheme 2. Unfortunately, reaction of **1**{*1*} with **2**{*2*} under pyrrolidine **3d**-catalysis at 70 °C in DMSO or DMF furnished the only CS product **4**{*1,2*} in 30% yields without CS/IA (Scheme 2). These results suggest that the basic nature of amine **3**, the electronic nature of substrates **1/2**, and also the reaction temperature are important for the iso-aromatization of CS products **4**.

With an efficient piperidine-catalyzed iso-aromatization protocol in hand, we continued our investigation for the synthesis of functionalized phenols **5** from Hagemann's esters **1**{*1*}/**1**{*14*} and benzaldehyde **2**{*2*} under piperidine-catalysis in DMSO at 70 °C for 18 h through cascade CS/IA reactions as shown in Scheme 2. Cascade products **5**{*1,2*} and **5**{*14,2*} were furnished in moderate yields without

Scheme 2. Controlled Experiments on Base-Induced Iso-Aromatization of 3-Arylidene-Hagemann's Ester **4** via Amine-Catalysis



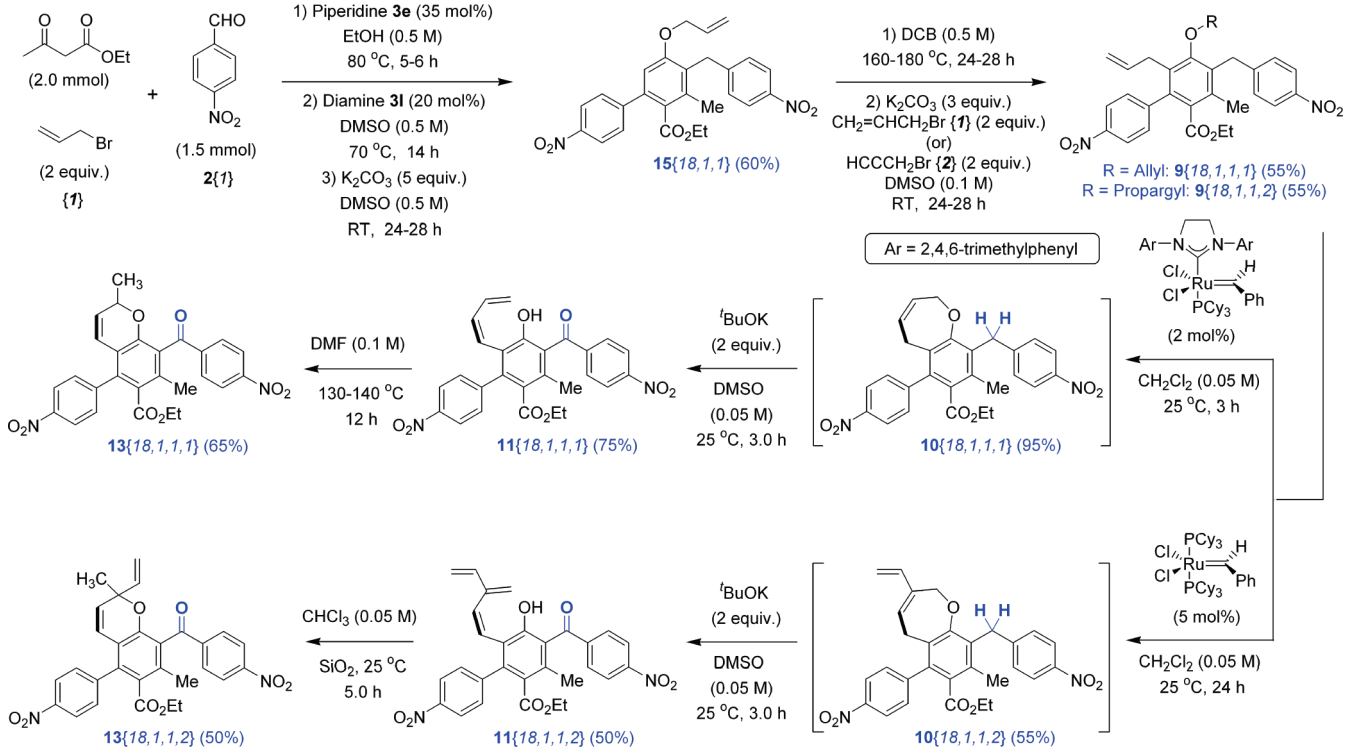
showing much of electronic factors in CS/IA reaction as shown in Scheme 2. Functionalized phenols are of considerable importance in a variety of industries. These compounds **5** are widespread elements in natural products and have attracted much attention from a wide area of science, including physical chemistry, medicinal chemistry, natural product chemistry, synthetic organic chemistry, and polymer science.[4] As such, the development of new and more general catalytic methods for their preparation is of significant interest, and our presently developed cascade chemistry will be useful to develop a library of substituted phenols in very good yields with high selectivity.

C. Sequential Cascade Synthesis of Substituted 2-Methyl-2*H*-Chromenes through MCC Reactions Based on CS/IA Platform. Stereoselective and economical synthesis of highly functionalized 2-methyl-2*H*-chromenes is an evergreen task in synthetic organic chemistry.[5] As part of our research program to engineer direct multicatalysis cascade (MCC) reactions in a sequential manner to deliver the highly functionalized molecules and also based on the demand of pharmaceutical applications, we extended the two-component cascade K/M/A/DC/CS/IA and CS/IA reactions into novel piperidine-/diamine-/K_2CO_3- or glycine-/piperidine-/K_2CO_3-catalyzed three-component K/M/A/DC/CS/IA/A and CS/IA/A reaction of ethyl acetoacetate, 4-nitrobenzaldehyde **2**{*1*}, and allyl bromide {***1***} or Hagemann's esters **1**{*1*}/**1**{*14*}, benzaldehydes **2**{*1*}/**2**{*2*}, and allyl bromide {***1***}, respectively, in one-pot, and the resulting products **15** were converted into 2-methyl-2*H*-chromenes **13** and **14** with very good yields via four novel synthetic steps [Claisen rearrangement, *O*-allylation or *O*-propargylation, RCM/BIRO/BO or RCM/BIRO and [1,7]-SHS] as shown in Schemes 3/4. MCC products **13** and **14** were constructed in very good yields with high selectivity, and this method will be showing much impact on the synthesis of functionalized small molecules with quaternary carbon as shown in Schemes 3 and 4. Highly substituted 2-methyl-2*H*-chromenes **13** and **14** type compounds have gained importance in recent years as they would be good starting materials and intermediates for the synthesis of biologically active compounds, for example, precocene insect growth regulators **B**, melatonin receptor agonists **C**, anticancer agents **D**, and NMDA antagonists **E**.[5]

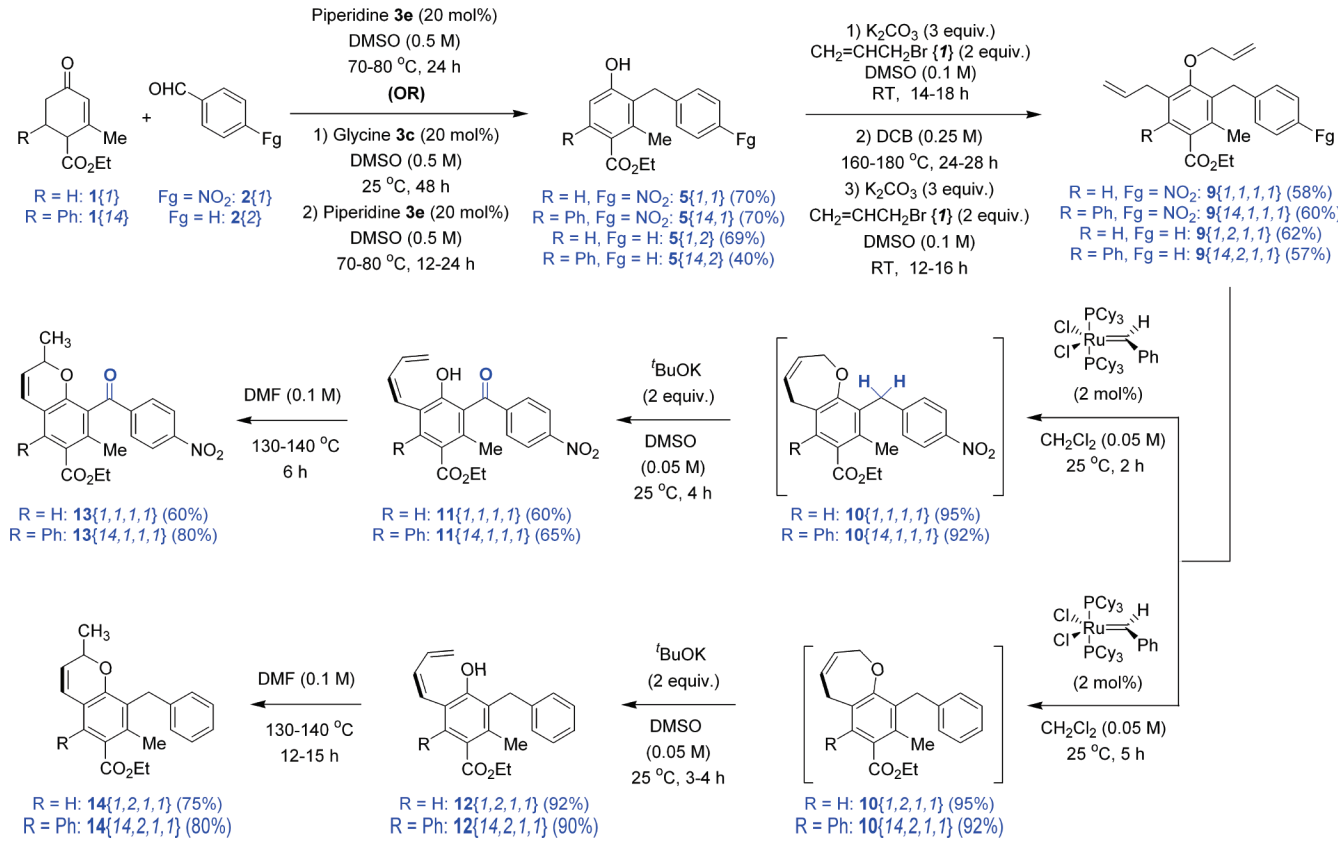
Sequential cascade K/M/A/DC/CS/IA reaction of 2.0 equiv of ethyl acetoacetate with 1.5 equiv of 4-nitrobenzaldehyde **2**{*1*} under 35 mol % of piperidine-catalysis followed by 20 mol % of diamine-catalysis furnished the compound **5**{*18,1*} with >99% conversion, which on in situ treatment with allyl bromide {***1***} at 25 °C for 24−28 h furnished the chemoselectively K/M/A/DC/CS/IA/A product **15**{*18,1,1*} with 60% yield as shown in Scheme 3. Claisen rearrangement of **15**{*18,1,1*} in DCB at 160−180 °C for 24 h furnished the expected allylated-phenol **15′**{*18,1,1*} in good yield, which on *O*-allylation with allyl bromide {***1***} and *O*-propargylation with propargyl bromide {***2***} under K_2CO_3 in DMSO at 25 °C for 24−28 h furnished the functionalized diene **9**{*18,1,1,1*} in 55% yield and enyne **9**{*18,1,1,2*} in 55% yield, respectively. Interestingly, RCM reaction of diene **9**{*18,1,1,1*} using 2 mol % of Grubbs' first generation catalyst [$Cl_2Ru{=}CHPh(PCy_3)_2$] in CH_2Cl_2 at 25 °C for 2−3 h furnished the benzo[*b*]oxepine **10**{*18,1,1,1*} in >99% conversion, which on in situ treatment with 2.0 equiv of *t*BuOK in DMSO at 25 °C for 3 h furnished the functionalized (*Z*)-2-(buta-1,3-dienyl)phenol **11**{*18,1,1,1*} in only 56% yield through cascade base-induced ring-opening (BIRO) and benzylic oxidation (BO)[11] reactions in one-pot with >99% *Z*-selectivity (result not shown in Scheme 3). But the same sequential cascade RCM/BIRO/BO reactions of **9**{*18,1,1,1*} under the 2 mol % of Grubbs' second generation catalyst followed by treatment with 2.0 equiv of *t*BuOK furnished the functionalized (*Z*)-2-(buta-1,3-dienyl)phenol **11**{*18,1,1,1*} in improved yield (75%) with >99% *Z*-selectivity as shown in Scheme 3. Herein, we also tested the in situ BIRO reaction induced by 2.0 equiv of NaH, but reaction yield (66%) is not superior as compared to *t*BuOK as base (result not shown in Scheme 3). Further reaction of **11**{*18,1,1,1*} in DMF at 130−140 °C for 12 h furnished the substituted 2-methyl-2*H*-chromene **13**{*18,1,1,1*} in 65% yield via [1,7]-SHS reaction as shown in Scheme 3. We envisioned the optimized condition to be addition of 2 equiv of *t*BuOK to the mixture of in situ generated **10**{*18,1,1,1*} in DMSO at 25 °C to furnish substituted (*Z*)-2-(buta-1,3-dienyl)phenol **11**{*18,1,1,1*} in 75% yield with >99% *Z*-selectivity, which on further heating in DMF at 130−140 °C for 12 h furnished the substituted 2-methyl-2*H*-chromene **13**{*18,1,1,1*} in 65% yield (Scheme 3).

With the optimized reaction conditions in hand, the scope of the ruthenium- and base-induced RCM/BIRO/BO sequential one-pot reactions was investigated with variety of functionalized enyne **9** and dienes **9** as shown in Schemes 3 and 4. Interestingly, enyne metathesis followed by base-induced ring-opening and benzylic

Scheme 3. Rapid Five-step Synthesis of Highly Functionalized 2-Methyl-2*H*-chromenes via Sequential Combination of Multi-catalysis Cascade Reactions



Scheme 4. Rapid Six-step Synthesis of Highly Functionalized 2-Methyl-2*H*-chromenes via Sequential Combination of Multi-catalysis Cascade Reactions



oxidation of enyne **9**{*18,1,1,2*} furnished the expected product (*Z*)-2-(buta-1,3-dienyl)phenol **11**{*18,1,1,2*} in good yield, which on further treatment with silica gel in $CHCl_3$ at 25 °C for 5 h furnished the 2-methyl-2*H*-chromene **13**{*18,1,1,2*} in 50% yield with quaternary carbon (Scheme 3).

To demonstrate the further scope of the ruthenium- and base-induced RCM/BIRO/BO sequential one-pot reactions

and also to test the role of electronic factors in BO reactions, we synthesized simple dienes **9**{*1,1,1,1*}, **9**{*14,1,1,1*}, **9**{*1,2,1,1*}, and **9**{*14,2,1,1*} from corresponding Hagemann's esters **1**{*1*}/**1**{*14*}, benzaldehydes **2**{*1*}/**2**{*2*}, and allyl bromide {***1***} through CS/IA/A, Claisen rearrangement/O-allylation sequence with good yields as shown in Scheme 4. Sequential one-pot treatment of dienes **9**{*1,1,1,1*}/**9**{*14,1,1,1*} containing single *p*-nitro group on phenyl rings with 2 mol % of Grubbs' first generation catalyst followed by treatment with 2.0 equiv of *t*BuOK furnished the functionalized (*Z*)-2-(buta-1,3-dienyl)phenols **11**{*1,1,1,1*}/**11**{*14,1,1,1*} in 60/65% yield, respectively, with >99% *Z*-selectivity via RCM/BIRO/BO reactions, which are transformed into substituted 2-methyl-2*H*-chromenes **13**{*1,1,1,1*}/**13**{*14,1,1,1*} in 60/80% yields respectively via [1,7]-SHS reaction induced by heat as shown in Scheme 4. Interestingly, RCM reaction of diene **9**{*1,2,1,1*} using 2 mol % of Grubbs' first generation catalyst in CH_2Cl_2 at 25 °C for 5 h furnished the benzo[*b*]oxepine **10**{*1,2,1,1*} in >99% conversion, which on in situ treatment with 2.0 equiv of *t*BuOK in DMSO at 25 °C for 3 h furnished the functionalized (*Z*)-2-(buta-1,3-dienyl)phenol **12**{*1,2,1,1*} in 92% yield through BIRO reaction in one-pot with >99% *Z*-selectivity without oxidation of benzylic methylene (Scheme 4). In a similar manner, we synthesized one more functionalized (*Z*)-2-(buta-1,3-dienyl)phenol **12**{*14,2,1,1*} in 90% yield through sequential RCM/BIRO reactions in one-pot with >99% *Z*-selectivity without oxidation of benzylic methylene (Scheme 4). Two of the RCM/BIRO products, (*Z*)-2-(buta-1,3-dienyl)phenols **12**{*1,2,1,1*}/**12**{*14,2,1,1*} were converted into the substituted 2-methyl-2*H*-chromenes **14**{*1,2,1,1*}/**14**{*14,2,1,1*} in 75/80% yields, respectively, via [1,7]-SHS reaction induced by heat as shown in Scheme 4. As revealed in Schemes 3 and 4, oxidation of benzylic methylenes is completely controlled by electronic factors of substrates under the base-catalysis with air. For the pharmaceutical applications, the diversity-oriented library of small molecules **13/14** could be generated by using our presently discovered MCC technology.

Mechanistic Insights. The possible reaction mechanisms for the synthesis of push−pull olefins **4**, push−pull phenols **5**, (*E*)-1,3-dienes **7**, and 2-methyl-2*H*-chromenes **13/14** via dienamine-catalysis are illustrated in Schemes 5 and 6 and Supporting Information, Figure S1. First, reaction of amino acids **3a**−**c**, or amines (pyrrolidine **3d**, piperidine **3e**, or (*S*)-diamine **3l**) with the aldehyde **2** generates the imine cation **18**, an excellent electrophile that undergoes Mannich type reactions with the in situ generated push−pull dienamine **17** or dienolate **22**{*1*} of Hagemann's ester **1**{*1*} to generate Mannich products **19** and **23**, respectively, as shown in mechanism 1 and 2 of Scheme 5 (for the purpose of clarity, we represented **3d** as catalyst). Elimination reaction of pyrrolidinium ions **20** and **24** would furnish selectively *E*/*Z* mixtures of push−pull olefin **4**. Base-induced, electronically- and temperature-controlled iso-aromatization (IA) of the CS product **4** would then give push−pull phenol **5** as shown in mechanism 1 and 2 of Scheme 5. The formation of imine ion **18** and CS product **4** via Mannich and amine-elimination reactions supports our hypothesis that aldol products did not form in these reactions and also formation of the highly reactive push−pull dienamines **17**{*1,a*} and **17**{*1,d*} were established through NMR experiments as shown in Scheme 6 and Supporting Information, Figure S1. We favor mechanism 1 based on in situ NMR experiments.

As shown in Scheme 6, in situ generation of novel push−pull dienamine **17**{*1,a*} from **1**{*1*} and **3a** is a slow process as compared to **17**{*1,d*} from **1**{*1*} and **3d**, and a similar kind of reactivity pattern is represented in their reactions also as shown in Tables 1−7. Highly selective in situ formation of push−pull dienamines **17**{*1,a*} and **17**{*1,d*} over the Barbas dienamines (2-amino-1,3-butadienes)[12] **27**{*1,a*} and **27**{*1,d*} were established based on NMR and mass analysis as shown in Scheme 6. Presently discovered relatively stable push−pull dienamine **17**{*1,a*} formation from Hagemann's ester **1**{*1*} and amino acid, L-proline **3a** is very good supportive to the recently proposed enamine mechanism in proline-catalyzed asymmetric reactions[13] as revealed in Scheme 6 and Supporting Information, Figure S1.

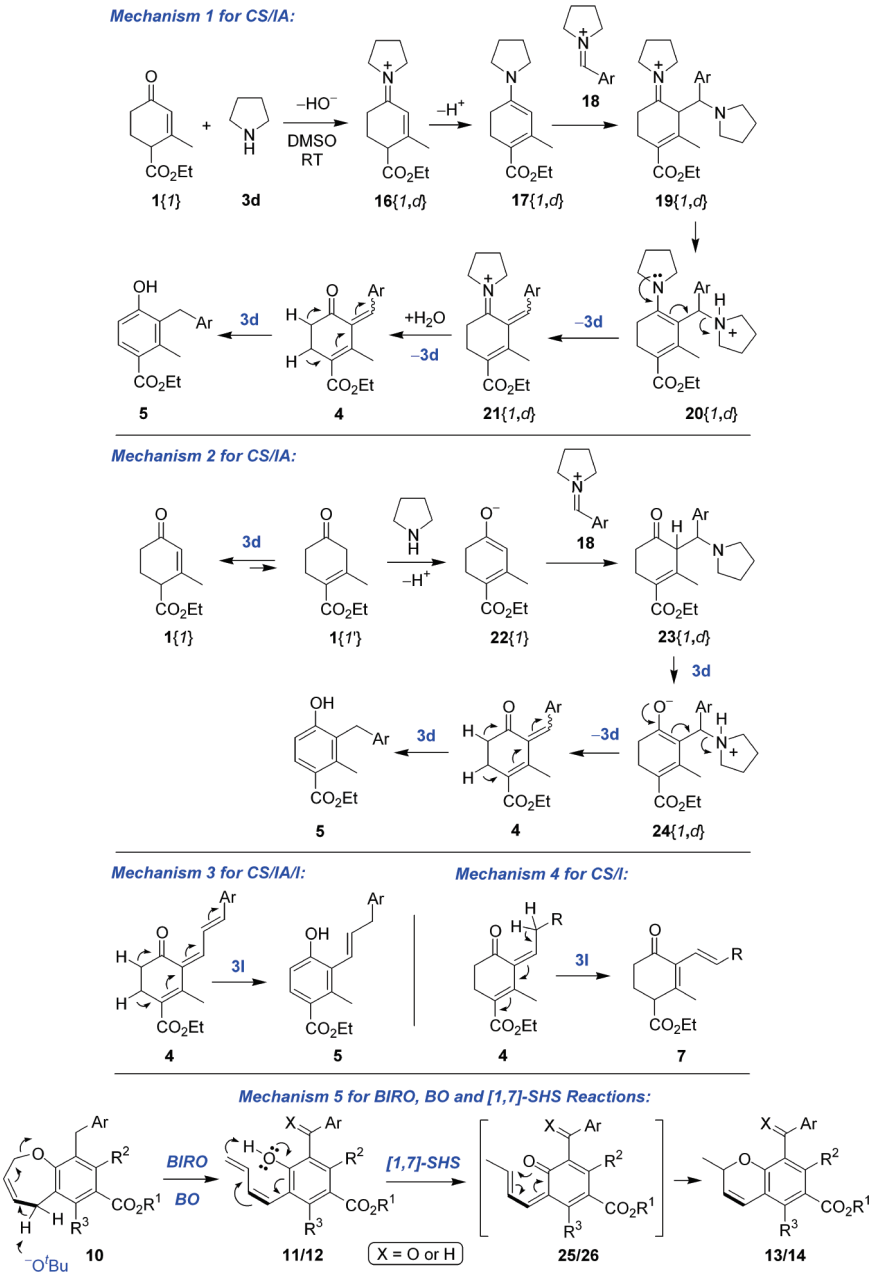
Next, the possible mechanism for regioselective synthesis of cascade CS/IA/I and CS/I products, *ortho*-vinylated phenols **5** and (*E*)-1,3-dienes **7** through reaction of Hagemann's ester **1**{*1*}, aldehydes **2**, and diamine **3l** is illustrated in mechanism 3 and 4 of Scheme 5. Treatment of in situ generated CS product, push−pull trienone (arylidene-Hagemann's ester) **4** under the amine-catalysis furnished the *ortho*-vinylated phenol **5** via IA/I reaction. In a similar manner, reaction of in situ generated CS product, push−pull dienone (alkylidene-Hagemann's ester) **4** under the base-catalysis furnished the unexpected (*E*)-1,3-dienes **7** via I reaction as shown in Scheme 5. These two kinds of isomerizations (I) on **4** through diamine-catalysis were completely controlled by electronic factors and acidic nature of hydrogens as shown in Scheme 5.

The possible reaction mechanism for BIRO/BO/[1,7]-SHS reaction sequence is illustrated in mechanism 5 of Scheme 5. First, reaction of **10** with KO^{t}Bu generates the carbanion because of the acidic nature of allylic/benzylic hydrogen, which will further rearrange into the ring opened product *cis*-**11** (X = O) and *cis*-**12** (X = H) through concerted pathway. In a similar time, dibenzylic methylene oxidized to ketone with air under base-catalysis in compounds **10** via electron transfer reactions may be due to the highly electron withdrawing nature of both aryls connected to methylene. A [1,7]-sigmatropic shift of the phenolic hydrogen in *cis*-**11** (X = O) and *cis*-**12** (X = H) gave to the *ortho*-quinone methides **25** (X = O) and **26** (X = H), which rapidly cyclizes to **13** (X = O) and **14** (X = H) under the standard reaction conditions to regain the thermodynamic stability through oxa-6π electrocyclization or [3,3]-rearrangement.

Conclusions

In summary, we have developed the sequential one-pot combination of amino acid-, amine-, K_2CO_3-, [Ru]-, KO^{t}Bu-, or SiO_2-catalyzed direct cascade CS, CS/IA, CS/IA/I, CS/I, M, CS/M, K/M/A/DC/CS/IA, K/M/A/DC/CS/IA/A, RCM/BIRO/BO, RCM/BIRO, and [1,7]-SHS reactions from simple substrates. This experimentally simple cascade approach can be used to construct a diversity-oriented library of highly

Scheme 5. Proposed Reaction Mechanisms for Push-Pull Dienamine Chemistry



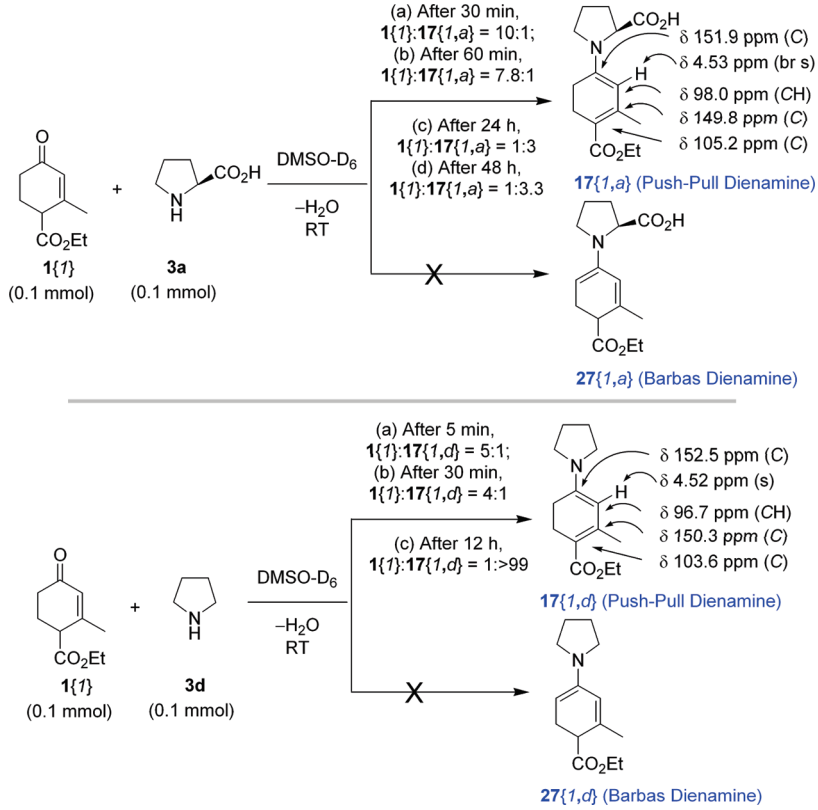
substituted push−pull olefins, phenols, and 2-methyl-2*H*-chromenes with good yields in a selective fashion. We have demonstrated the in situ generation and application of novel push−pull dienamines in sequential cascade chemistry. Further work is in progress to utilize an asymmetric version of this cascade processes and also for the application in total synthesis of natural products.

Experimental Section

General Experimental Procedures for the MCC Reactions. Glycine-Catalyzed Claisen−Schmidt Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **1**{*1*} was added 1.0 mL of DMSO solvent, then the catalyst glycine **3c** (0.1 mmol, 7.5 mg) was added, and then 0.5 mmol of aldehyde **2**{*2*}-**2**{*19*} was added in one-portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 2. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure products **4**{*1,2*}-{*1,19*} were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 2-Methyl-4-oxo-3-(4-trifluoromethyl-benzylidene)-cyclohex-1-enecarboxylate (4{*1,6*}). Light yellow solid, yield 81%. Mp 54 °C; IR (neat): ν_{max} 2984, 1703 (C═O and O−C═O), 1456, 1324, 1241, 1168, 1126, 1064, 1017, and 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 2:1 ratio of *E/Z* isomers): δ 7.59 (4H, d, J = 8.4 Hz), 7.53 (2H, d, J = 8.0 Hz), 7.44−7.40 (3H, m), 6.95 (1H, s, olefinic-*H*), 4.26 (4H, q, J = 7.2 Hz, 2 × OCH_2CH_3), 2.83−2.78 (4H, m), 2.68 (2H, t, J = 6.4 Hz), 2.47 (2H, t, J = 6.4 Hz), 2.24 (3H, s, olefinic-CH_3), 1.94 (3H, s, olefinic-CH_3), 1.33 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.32 (3H, t, J = 7.2 Hz,

Scheme 6. NMR Experiment for the Detection of In Situ Generated Push-Pull Dienamines **17**



OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, 2:1 ratio of *E/Z* isomers): δ 201.4 (C, C═O), 200.5 (C, C═O), 168.4 (C, O−C═O), 167.1 (C, O−C═O), 142.6 (C), 139.9 (C), 139.5 (C), 139.3 (C), 138.9 (C), 138.1 (C), 134.8 (CH), 134.4 (CH), 131.2 (C), 130.8 (CF_3, q, J = 33.0 Hz), 129.9 (2 × CH), 129.6 (C), 129.4 (2 × CH), 125.2 (2 × CH, q, J = 3.0 Hz), 124.9 (2 × CH, q, J = 3.0 Hz), 122.6 (C), 122.4 (C), 60.9 (CH_2, OCH_2CH_3), 60.8 (CH_2, OCH_2CH_3), 39.3 (CH_2), 34.7 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 20.4 (CH_3, olefinic-CH_3), 16.5 (CH_3, olefinic-CH_3), 14.2 (2 × CH_3, OCH_2CH_3); LRMS *m/z* 338.30 (M^+), calcd $C_{18}H_{17}F_3O_3$ 338.1130; Anal. Calcd for $C_{18}H_{17}F_3O_3$ (338.11): C, 63.90; H, 5.06. Found: C, 63.85; H, 5.12%.

Pyrrolidine-Catalyzed Claisen−Schmidt and Michael Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **1**{*1*} was added 1.0 mL of DMF solvent, then the catalyst pyrrolidine **3d** (0.1 mmol, 8.33 μL) was added, and then 0.5 mmol of aldehyde **2**{*2*}-**2**{*20*} was added in one-portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 2. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure products **4** and **6** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 3-(4-Bromobenzylidene)-2-methyl-4-oxo-cyclohex-1-enecarboxylate (4{*1,15*}). Yellow liquid, yield 35%. IR (neat): ν_{max}1692 (C═O and O−C═O), 1594, 1270, 1242, 1196, 1055, 652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 3.5:1 ratio of *E/Z* isomers): δ 7.56 (1H, s, olefinic-*H*), 7.50 (2H, br d, J = 8.4 Hz), 7.44 (2H, br d, J = 8.4 Hz), 7.28 (2H, br d, J = 8.4 Hz), 7.20 (2H, br d, J = 8.0 Hz), 6.88 (1H, s, olefinic-*H*), 4.28 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.27 (2H, q, J = 7.2 Hz, OCH_2CH_3), 2.86−2.78 (4H, m), 2.70 (2H, t, J = 6.4 Hz), 2.48 (2H, t, J = 6.4 Hz), 2.25 (3H, t, J = 2.0 Hz, olefinic-CH_3), 2.00 (3H, t, J = 1.2 Hz, olefinic-CH_3), 1.36 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.34 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, 3.5:1 ratio of *E/Z* isomers): δ 201.4 (C, C═O), 200.8 (C, C═O), 168.4 (C, O−C═O), 167.1 (C, O−C═O), 143.1 (C), 140.5 (C), 138.1 (C), 137.1 (C), 135.5 (CH), 135.0 (CH), 134.4 (C), 134.0 (C), 131.6 (2 × CH), 131.3 (2 × CH), 131.2 (2 × CH), 131.1 (2 × CH), 130.6 (C), 128.8 (C), 123.6 (C), 122.8 (C), 60.8 (CH_2, OCH_2CH_3), 60.7 (CH_2, OCH_2CH_3), 39.3 (CH_2), 34.8 (CH_2), 27.2 (CH_2), 23.1 (CH_2), 20.3 (CH_3, olefinic-CH_3), 16.6 (CH_3, olefinic-CH_3), 14.24 (CH_3, OCH_2CH_3), 14.19 (CH_3, OCH_2CH_3); LRMS *m/z* 349.00 ($M + H^+$), calcd $C_{17}H_{17}BrO_3$ 348.0361; Anal. Calcd for $C_{17}H_{17}BrO_3$ (348.03): C, 58.47; H, 4.91. Found: C, 58.41; H, 4.95%.

(*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-Catalyzed Claisen−Schmidt Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **1**{*1*} was added 1.0 mL of DMF solvent, then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** (0.1 mmol, 16.3 μL) was added, and then 0.5 mmol of aldehyde **2**{*2*}-**2**{*21*} was added in one-portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 2. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure products

4 were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 2-Methyl-3-(3-methylbut-2-enylidene)-4-oxo-cyclohex-1-enecarboxylate (4{*1,21*}). Red liquid, yield 60%. IR (neat): ν_{max}2978, 2930, 1713 (C═O), 1684 (O−C═O), 1597, 1447, 1372, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:5 ratio of *E/Z* isomers, major isomer): δ 7.53 (1H, d, J = 12.8 Hz), 6.29 (1H, d, J = 12.8 Hz), 4.26 (2H, q, J = 7.2 Hz, OCH_2CH_3), 2.66 (2H, br t, J = 6.4 Hz), 2.43 (2H, t, J = 6.4 Hz), 2.38 (3H, s, olefinic-CH_3), 1.98 (3H, s), 1.96 (3H, s), 1.34 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, 1:5 ratio of *E/Z* isomers, major isomer): δ 201.5 (C, C═O), 167.7 (C, O−C═O), 150.9 (C), 143.9 (C), 133.5 (C), 133.2 (CH), 128.1 (C), 122.3 (CH), 60.5 (CH_2, OCH_2CH_3), 35.9 (CH_2), 27.6 (CH_3), 23.1 (CH_2), 21.6 (CH_3), 18.9 (CH_3, olefinic CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS *m/z* 249.15 ($M + H^+$), calcd $C_{15}H_{20}O_3$ 248.1412; Anal. Calcd for $C_{15}H_{20}O_3$ (248.14): C, 72.55; H, 8.12. Found: C, 72.61; H, 8.08%.

(*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-Catalyzed Cascade Claisen−Schmidt and Iso-Aromatization Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's esters **1**{*1*}-{*19*} was added 1.0 mL of DMSO solvent, then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** (0.1 mmol, 16.3 μL) was added, and then 0.5 mmol of aldehydes **2**{*1*}-{*22*} was added in one-portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 3. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure cascade products **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 4-Hydroxy-2-methyl-3-(4-trifluoromethylbenzyl)-benzoate (5{*1,6*}). White solid, yield 70%. Mp 120 °C; IR (neat): ν_{max} 3347 (O-*H*), 1681 (O−C═O), 1580, 1326, 1262, 1156, 1112, 1068, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 25 °C): δ 7.72 (1H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz), 6.75 (1H, d, J = 8.8 Hz); 6.74(1H, s, O-*H*), 4.34 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.17 (2H, s, CH_2Ar), 2.47 (3H, s, Ar−CH_3), 1.38 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, at 40 °C): δ 168.8 (C, O−C═O), 157.3 (C), 144.2 (C), 141.1 (C), 130.7 (CH), 128.4 (2 × CH), 128.3 (CF_3, q, J = 32.0 Hz), 126.0 (C), 125.2 (2 × CH, q, J = 4.0 Hz), 123.8 (C), 123.0 (C), 112.6 (CH), 60.9 (CH_2, OCH_2CH_3), 31.6 (CH_2, CH_2Ar), 17.0 (CH_3, Ar-CH_3), 14.2 (CH_3, OCH_2CH_3); LRMS *m/z* 339.00 ($M + H^+$), calcd $C_{18}H_{17}F_3O_3$ 338.1130; Anal. Calcd for $C_{18}H_{17}F_3O_3$ (338.11): C, 63.90; H, 5.06. Found: C, 63.85; H, 5.11%.

(*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-Catalyzed Cascade Claisen−Schmidt and Isomerization Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the Hagemann's ester **1**{*1*} was added 1.0 mL of DMSO solvent, then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** (0.1 mmol, 16.3 μL) was added, and then 0.5 mmol of aldehyde **2**{*23*}-**2**{*29*} was added in one-portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 4. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure cascade products **7** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl (3*R*)-3-(3,7-dimethylocta-1,6-dienyl)-2-methyl-4-oxo-cyclohex-2-enecarboxylate (7{*1,23*}). Colorless oily liquid, yield 65%. $[\alpha]^{25}_D = -43.6$ (*c* 0.54, $CHCl_3$); IR (neat): ν_{max}2960, 2912, 1730 (C═O), 1673 (O−C═O), 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers, at 25 °C): δ 6.02 (2H, d, J = 16.0 Hz), 5.76 (2H, dd, J = 16.0, 8.0 Hz), 5.08 (2H, t, J = 7.2 Hz), 4.19 (4H, q, J = 7.2 Hz, 2 × OCH_2CH_3), 3.33 (2H, t, J = 4.8 Hz), 2.64−2.55 (2H, m), 2.38 (2H, td, J = 16.8, 5.6 Hz), 2.27−2.18 (4H, m), 2.05 (6H, s, 2 × olefinic-CH_3), 1.98 (4H, m), 1.66 (6H, s, 2 × CH_3), 1.58 (6H, s, 2 × CH_3), 1.35 (4H, m), 1.27 (6H, t, J = 7.2 Hz, 2 × OCH_2CH_3), 1.02 (6H, d, J = 6.8 Hz, 2 × $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, 1:1 mixture of diastereomers, at 25 °C): δ 197.3 (2 × C, C═O), 172.2 (2 × C, O−C═O), 149.6 (2 × C), 143.6 (CH), 143.5 (CH), 134.9 (2 × C), 131.2 (2 × C), 124.5 (2 × CH), 120.5 (2 × CH), 61.2 (2 × CH_2, OCH_2CH_3), 48.1 (CH), 48.0 (CH), 37.5 (2 × CH), 36.9 (2 × CH_2), 35.22 (CH_2), 35.16 (CH_2), 25.8 (2 × CH_2), 25.7 (2 × CH_3, olefinic-CH_3), 25.2 (2 × CH_2), 21.5 (2 × CH_3, olefinic-CH_3), 20.4 (2 × CH_3, olefinic-CH_3), 17.6 (2 × CH_3), 14.1 (2 × CH_3, OCH_2CH_3); ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers, at −40 °C): δ 6.07 (1H, d, J = 16.4 Hz), 6.06 (1H, d, J = 16.4 Hz), 5.70 (1H, dd, J = 8.0, 4.0 Hz), 5.66 (1H, dd, J = 8.4, 4.0 Hz), 5.11 (2H, t, J = 6.4 Hz), 4.22 (4H, q, J = 7.2 Hz, 2 × OCH_2CH_3), 3.41 (2H, br s), 2.66−2.58 (2H, m), 2.45 (2H, td, J = 17.2, 4.8 Hz), 2.27−2.24 (4H, m), 2.10 (6H, s, 2 × olefinic-CH_3), 2.03−1.95 (4H, m), 1.70 (6H, s, 2 × CH_3), 1.61 (6H, s, 2 × CH_3), 1.38−1.30 (10H, m), 1.05 (6H, d, J = 6.4 Hz, 2 × $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, 1:1 mixture of diastereomers, at −40 °C): δ 198.16 (C, C═O), 198.13 (C, C═O), 172.4 (C, O−C═O), 172.3 (C, O−C═O), 150.5 (2 × C), 143.7 (CH), 143.6 (CH), 134.8 (2 × C), 131.6 (2 × C), 124.2 (2 × CH), 120.4 (CH), 120.3 (CH), 61.4 (2 × CH_2, OCH_2CH_3), 47.8 (CH), 47.6 (CH), 37.6 (CH), 37.5 (CH), 36.7 (2 × CH_2), 35.1 (CH_2), 34.9 (CH_2), 25.84 (2 × CH_2), 25.80 (2 × CH_3, olefinic-CH_3), 25.0 (CH_2), 24.9 (CH_2), 22.01 (CH_3, olefinic-CH_3), 21.98 (CH_3, olefinic-CH_3), 20.60 (CH_3, olefinic-CH_3), 20.55 (CH_3, olefinic-CH_3), 17.7 (2 × CH_3), 14.1 (2 × CH_3, OCH_2CH_3); LRMS *m/z* 319.30 ($M + H^+$), calcd $C_{20}H_{30}O_3$ 318.2195; Anal. Calcd for $C_{20}H_{30}O_3$ (318.21): C, 75.43; H, 9.50. Found: C, 75.52; H, 9.48%.

Piperidine-Catalyzed Cascade Claisen−Schmidt and Michael Reactions. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **1** was added 1.5 mL of DMSO solvent, then the catalyst piperidine **3e** (0.05 mmol, 4.93 μL) was added, and then 0.25 mmol of formaldehyde **2**{*30*} (37 wt % solution in water) was added in one-portion, and the reaction mixture was stirred at 25 °C for the time indicated in Table 6. The crude reaction mixture was worked up with aqueous NH_4Cl

solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure cascade products **8** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Diethyl 3,3′-Methylenebis(2-methyl-4-oxocyclohex-2-enecarboxylate) (8{*1,30*}). Colorless oily liquid, yield 80%. IR (neat): ν_{max}2928, 2859, 1728 (C═O), 1667 (O−C═O), 1622, 1512, 1451, 1372, 1157, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, >99:1 ratio of diastereomers): δ 4.18 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.17 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.44 (2H, d, J = 12.8 Hz), 3.28 (1H, t, J = 4.8 Hz), 3.27 (1H, t, J = 4.8 Hz), 2.59−2.50 (2H, m), 2.40−2.32 (2H, m), 2.26−2.13 (4H, m), 2.00 (3H, s, olefinic-CH_3), 1.95 (3H, s, olefinic-CH_3), 1.28 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.27 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135, >99:1 ratio of diastereomers): δ 197.0 (C, C═O), 196.9 (C, C═O), 172.2 (C, O−C═O), 172.1 (C, O−C═O), 150.8 (C), 150.7 (C), 135.8 (C), 135.7 (C), 61.1 (2 × CH_2, OCH_2CH_3), 48.2 (CH), 48.1 (CH), 34.6 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 22.3 (CH_2), 21.8 (CH_2), 21.0 (2 × CH_3, olefinic-CH_3), 14.1 (2 × CH_3, OCH_2CH_3); LRMS m/z 377.25 ($M + H^+$), calcd $C_{21}H_{28}O_6$ 376.1886; Anal. Calcd for $C_{21}H_{28}O_6$ (376.18): C, 67.00; H, 7.50. Found: C, 67.49; H, 7.54%.

Sequential Combination of Piperidine-Catalyzed Cascade Knoevenagel/Michael/Aldol Condensation/Decarboxylation and (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-Catalyzed Claisen−Schmidt/Iso-Aromatization Reactions in One-Pot. To a stirred solution of ethyl acetoacetate (2.0 mmol) and aldehyde (1.0 mmol) in EtOH (2 mL) was added a catalytic amount of piperidine **3e** (0.35 mmol, 35 mol %) and the reaction mixture was stirred at 80 °C for 5−6 h. Solvent ethanol and piperidine was evaporated by vacuum pump, then solvent DMSO (1 mL) was added, and catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** (0.1 mmol, 16.3 μL), aldehyde **2** (0.5 mmol) were added, and the reaction mixture was stirred at 25 °C for 13−24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure one-pot products **5** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 5-Hydroxy-3-methyl-4-(4-nitrobenzyl)-biphenyl-2-carboxylate (5{*14,1*}). Liquid, yield 80%. IR (neat): ν_{max} 3403 (O-*H*), 2978, 2930, 1688 (O−C═O), 1597, 1518, 1344, 1263, 1171, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, J = 8.4 Hz), 7.28−7.24 (7H, m); 6.69 (1H, br s, O-*H*), 6.59 (1H, s, Ar-*H*), 4.12 (2H, s, CH_2Ar), 4.00 (2H, q, J = 7.2 Hz, OCH_2CH_3), 2.21 (3H, s, Ar−CH_3), 0.90 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 170.9 (C, O−C═O), 154.8 (C), 148.0 (C), 146.1 (C), 140.4 (C), 140.3 (C), 136.2 (C), 128.9 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.4 (CH), 126.6 (C), 123.6 (C), 123.5 (2 × CH), 114.2 (CH), 61.3 (CH_2, OCH_2CH_3), 31.6 (CH_2, CH_2Ar), 16.7 (CH_3, Ar-CH_3), 13.4 (CH_3, OCH_2CH_3); LRMS m/z 390.15 ($M - H^+$), calcd $C_{23}H_{21}NO_5$ 391.1420; Anal. Calcd for $C_{23}H_{21}NO_5$ (391.14): C, 70.58; H, 5.41; N, 3.58. Found: C, 70.45; H, 5.45; N, 3.65%.

Base-Induced Iso-Aromatization of 3-Arylidene Hagemann's Esters: Synthesis of 5{*1,1*}. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.3 mmol of the 2-methyl-3-(4-nitrobenzylidene)-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester **4**{*1,1*} was added 0.6 mL of DMSO solvent, then the catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** (0.06 mmol, 9.7 μL) was added, and the reaction mixture was stirred at 25 °C for 0.5 h as indicated in Scheme 2. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure cascade product **5**{*1,1*} was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Synthesis of 5{*1,2*}. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.18 mmol of the 3-benzylidene-2-methyl-4-oxo-cyclohex-1-enecarboxylic acid ethyl ester **4**{*1,2*} was added 0.36 mL of DMSO solvent, then the catalyst piperidine **3e** (0.036 mmol, 3.55 μL) was added, and the reaction mixture was stirred at 70 °C for 12 h as indicated in Scheme 2. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure cascade product **5**{*1,2*} was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

One-Pot Synthesis of 5{*1,2*} and 5{*14,2*}. In an ordinary glass vial equipped with a magnetic stirring bar, to 1.0 mmol of the Hagemann's ester **1**{*1*} or **1**{*14*} was added 1.0 mL of DMSO solvent, then the catalyst piperidine **3e** (0.1 mmol, 9.87 μL) was added, and then 0.5 mmol of benzaldehyde **2**{*2*} was added in one-portion, and the reaction mixture was stirred at 70 °C for 18 h as indicated in Scheme 2. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The pure cascade products **5**{*1,2*} and **5**{*14,2*} were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 4-Benzyl-5-hydroxy-3-methyl-biphenyl-2-carboxylate (5{*14,2*}). Yellow liquid, yield 40%. IR (neat): ν_{max} 3403 (O-*H*), 2986, 2926, 1694 (O−C═O), 1589, 1452, 1263, 1173, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (5H, br s), 7.30−7.27 (3H, m), 7.21−7.19 (3H, m); 6.68 (1H, br s, O-*H*), 4.11 (2H, s, CH_2Ar), 4.01 (2H, q, J = 7.2 Hz, OCH_2CH_3), 2.30 (3H, s, Ar−CH_3), 0.92 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 170.4 (C, O−C═O), 154.5 (C), 140.7 (C), 139.9 (C), 139.2 (C), 136.4 (C), 128.5 (2 × CH), 128.2 (6 × CH), 127.3 (CH), 127.1 (C), 126.1 (CH), 124.8 (C), 114.4 (CH), 61.0 (CH_2, OCH_2CH_3), 31.7 (CH_2, CH_2Ar), 16.8 (CH_3, Ar-CH_3), 13.6 (CH_3, OCH_2CH_3); LRMS m/z 347.00 ($M + H^+$), calcd $C_{23}H_{22}O_3$ 346.1569; Anal. Calcd for $C_{23}H_{22}O_3$ (346.15): C, 79.74; H, 6.40. Found: C, 79.65; H, 6.47%.

Experimental Procedures for the Synthesis of Highly Functionalized 2-Methyl-2*H*-Chromenes. The synthesis of highly functionalized 2-methyl-2*H*-chromenes **13** and **14** from corresponding Hagemann's esters **1** involves the following five or six-step sequence.

Sequential Combination of Piperidine-Catalyzed Cascade Knoevenagel/Michael/Aldol Condensation/Decarboxylation, (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine-Catalyzed Cascade Claisen−Schmidt/Iso-Aromatization, and K_2CO_3-Catalyzed Alkylation Reactions in One-Pot. To a stirred solution of ethyl acetoacetate (2.0 mmol) and 4-nitrobenzaldehyde **2**{*1*} (1.0 mmol) in EtOH (2 mL) was added a catalytic amount of piperidine **3e** (0.35 mmol, 35 mol %), and the reaction mixture was stirred at 80 °C for 5−6 h. Solvent ethanol and piperidine were evaporated by vacuum pump, then solvent DMSO (1.0 mL) was added, and catalyst (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **3l** (0.1 mmol, 16.3 μL), 4-nitrobenzaldehyde **2**{*1*} (0.5 mmol) were added, and the reaction mixture was stirred at 25 °C for 14 h. To the crude reaction mixture were added 5 equiv of K_2CO_3 and 2 equiv of allyl bromide {***1***}, and stirred at 25 °C for 24−28 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **15**{*18,1,1*} is obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 5-Allyloxy-3-methyl-4′-nitro-4-(4-nitrobenzyl)-biphenyl-2-carboxylate (15{*18,1,1*}). Yellow liquid, yield 60%. IR (neat): ν_{max} 2980, 1722 (O−C═O), 1597, 1520, 1456, 1014, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (2H, d, J = 8.4 Hz), 8.08 (2H, d, J = 8.4 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 8.4 Hz), 6.79 (1H, s, Ar-*H*), 6.01−5.89 (1H, m, olefinic-*H*), 5.30 (1H, d, J = 17.2 Hz, olefinic-*H*), 5.23 (1H, d, J = 10.8 Hz, olefinic-*H*), 4.61 (2H, d, J = 4.8 Hz, $OCH_2CH{=}CH_2$), 4.25 (2H, s, $ArCH_2Ar$), 4.04 (2H, q, J = 7.2 Hz, OCH_2CH_3), 2.30 (3H, s, $Ar{-}CH_3$), 0.98 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 169.2 (C, O−C═O), 156.8 (C), 147.7 (C), 147.6 (C), 147.0 (C), 146.1 (C), 137.8 (C), 136.3 (C), 132.3 (CH), 129.1 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 123.4 (2 × CH), 123.3 (2 × CH), 117.6 (CH_2, $CH{=}CH_2$), 110.5 (CH), 69.0 (CH_2, $OCH_2CH{=}CH_2$), 61.1 (CH_2, OCH_2CH_3), 31.7 (CH_2), 16.7 (CH_3, Ar-CH_3), 13.5 (CH_3, OCH_2CH_3); LRMS *m*/*z* 475.00 ($M - H^+$), calcd $C_{26}H_{24}N_2O_7$ 476.1584; Anal. Calcd for $C_{26}H_{24}N_2O_7$ (476.15): C, 65.54; H, 5.08; N, 5.88. Found: C, 65.48; H, 5.12; N, 5.96%.

Sequential Cascade Claisen−Schmidt/Iso-Aromatization/Alkylation Reactions in One-Pot. In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the Hagemann's ester **1**{*1*} or **1**{*14*} was added 1.0 mL of DMSO solvent, then the catalyst glycine **3c** (0.1 mmol, 7.5 mg) was added, and then 0.5 mmol of benzaldehydes **2**{*1*} or **2**{*2*} was added in one-portion, and the reaction mixture was stirred at 25 °C for the 48 h. To the reaction mixture, catalyst piperidine **3e** (0.1 mmol) was added, and the reaction mixture was stirred at 70 °C for 12−24 h as indicated in Scheme 4. The in situ generated corresponding phenols **5** was allylated by treatment with allyl bromide (121.0 mg, 1.0 mmol) and K_2CO_3 (207.3 mg, 1.5 mmol) in DMSO (2 mL, 0.1 M) at room temperature for 14−18 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **15** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 4-Allyloxy-3-benzyl-2-methyl-benzoate (15{*1,2,1*}). Light yellow liquid, yield 55%. IR (neat): ν_{max} 2980, 1714 (O−C═O), 1649, 1591, 1454, 1051, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (1H, d, J = 8.4 Hz), 7.26 (2H, t, J = 5.2 Hz), 7.16 (1H, t, J = 6.8 Hz), 7.14 (2H, d, J = 7.2 Hz), 6.81 (1H, d, J = 8.4 Hz), 6.02−5.94 (1H, m, olefinic-*H*), 5.35 (1H, dd, J = 17.2, 1.6 Hz, olefinic-*H*), 5.25 (1H, dd, J = 10.4, 1.6 Hz, olefinic-*H*), 4.59 (2H, d, J = 4.8 Hz, $OCH_2CH{=}CH_2$), 4.35 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.20 (2H, s, $ArCH_2Ar$), 2.53 (3H, s, $Ar{-}CH_3$), 1.40 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 168.1 (C, O−C═O), 159.0 (C), 140.4 (C), 140.2 (C), 132.8 (CH), 130.2 (CH), 128.8 (C), 128.1 (2 × CH), 128.0 (2 × CH), 125.6 (CH), 123.9 (C), 117.2 (CH_2, $CH{=}CH_2$), 108.6 (CH), 68.8 (CH_2, $OCH_2CH{=}CH_2$), 60.4 (CH_2, OCH_2CH_3), 31.6 (CH_2), 16.9 (CH_3, Ar-CH_3), 14.3 (CH_3, OCH_2CH_3); LRMS *m*/*z* 311.00 ($M + H^+$), calcd $C_{20}H_{22}O_3$ 310.1569; Anal. Calcd for $C_{20}H_{22}O_3$ (310.15): C, 77.39; H, 7.14. Found: C, 77.56; H, 7.08%.

C-Allylation through Claisen Rearrangement. O-Allylated compounds (1.0 mmol) and solvent DCB (2.0 mL, 0.5 M) were taken in a sealed glass tube, and the mixture was heated at 160−180 °C under N_2 for 24 to 28 h. Upon cooling the reaction mixture to room temperature, the mixture was diluted with dichloromethane (10 mL), washed with aqueous NH_4Cl solution (2 mL) and brine (2 mL). The separated organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Pure *C*-allylated phenols were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 6-Allyl-5-hydroxy-3-methyl-4′-nitro-4-(4-nitrobenzyl)-biphenyl-2-carboxylate (15′{*18,1,1*}). Light yellow liquid, yield 60%. IR (neat): ν_{max} 3512 (O-*H*), 2935, 1720 (O−C═O), 1637, 1599, 1520, 1444, 1014, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (2H, d, J = 8.8 Hz), 8.13 (2H, d, J = 8.4 Hz), 7.43 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 5.96−5.80 (1H, m, olefinic-*H*), 5.54 (1H, s, O-*H*), 5.23 (1H, d, J = 10.4 Hz, olefinic-*H*), 5.10 (1H, d, J = 17.6 Hz, olefinic-*H*), 4.23 (2H, s, $ArCH_2Ar$), 3.92 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.15 (2H, d, J = 4.8 Hz, $CH_2CH{=}CH_2$), 2.24 (3H, s, $Ar{-}CH_3$), 0.93 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135) δ 169.2 (C, O−C═O), 153.8 (C), 147.6 (C), 147.3 (C), 146.3 (C), 145.8 (C), 137.0 (C), 134.8 (CH), 134.0 (C), 130.3 (2 × CH), 128.9 (2 × CH), 128.2 (C), 125.5 (C), 123.6 (2 × CH), 123.1 (2 × CH), 120.0 (C), 117.6 (CH_2, $CH{=}CH_2$), 61.0 (CH_2, OCH_2CH_3), 32.2 (CH_2), 32.1 (CH_2, $CH_2CH{=}CH_2$), 16.8 (CH_3, Ar-CH_3), 13.7 (CH_3, OCH_2CH_3); LRMS *m*/*z* 477.00 ($M + H^+$), calcd $C_{26}H_{24}N_2O_7$ 476.1584;

Anal. Calcd for $C_{26}H_{24}N_2O_7$ (476.15): C, 65.54; H, 5.08; N, 5.88. Found: C, 65.41; H, 5.12; N, 5.81%.

Method A: O-Allylation. The corresponding *C*-allylated phenols **15′** (1.0 mmol) were allylated by treatment with allyl bromide {***1***} (242.0 mg, 2.0 mmol) and K_2CO_3 (414.6 mg, 3.0 mmol) in DMSO (10 mL, 0.1 M) at room temperature for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **9** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 6-Allyl-5-allyloxy-3-methyl-4′-nitro-4-(4-nitrobenzyl)-biphenyl-2-carboxylate (9{*18,1,1,1*}). Light yellow liquid, yield 92%. IR (neat): ν_{max} 2924, 1726 (O−C═O), 1597, 1520, 1186, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (2H, d, J = 8.4 Hz), 8.15 (2H, d, J = 8.4 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 6.02−5.91 (1H, m, olefinic-*H*), 5.78−5.65 (1H, m, olefinic-*H*), 5.33 (1H, d, J = 17.2 Hz, olefinic-*H*), 5.22 (1H, d, J = 10.4 Hz, olefinic-*H*), 4.91 (1H, d, J = 10.0 Hz, olefinic-*H*), 4.66 (1H, d, J = 16.8 Hz, olefinic-*H*), 4.23 (4H, s, $OCH_2CH{=}CH_2$, $ArCH_2Ar$), 3.92 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.22 (2H, d, J = 5.2 Hz, $CH_2CH{=}CH_2$), 2.15 (3H, s, Ar−CH_3), 0.94 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 168.9 (C, O−C═O), 156.9 (C), 147.5 (C), 147.2 (C), 146.4 (C), 145.3 (C), 137.8 (C), 136.2 (CH), 133.7 (C), 132.9 (CH), 132.0 (C), 131.7 (C), 130.7 (2 × CH), 129.2 (C), 128.8 (2 × CH), 123.8 (2 × CH), 122.8 (2 × CH), 117.3 (CH_2, CH═CH_2), 115.8 (CH_2, CH═CH_2), 75.0 (CH_2, $OCH_2CH{=}CH_2$), 61.1 (CH_2, OCH_2CH_3), 32.7 (CH_2), 31.7 (CH_2, $CH_2CH{=}CH_2$), 16.9 (CH_3, Ar-CH_3), 13.7 (CH_3, OCH_2CH_3); LRMS *m*/*z* 516.00 (M^+), calcd $C_{29}H_{28}N_2O_7$ 516.1897; Anal. Calcd for $C_{29}H_{28}N_2O_7$ (516.18): C, 67.43; H, 5.46; N, 5.42. Found: C, 67.35; H, 5.36; N, 5.58%.

Method B: O-Propargylation. The enyne **9**{*18,1,1,2*} was prepared by treating the corresponding *C*-allylated phenol **15′**{*18,1,1*} (1.0 mmol) with propargyl bromide {***2***} (238.0 mg, 2.0 mmol) and K_2CO_3 (414.6 mg, 3.0 mmol) in DMSO (10 mL, 0.1 M) at room temperature for 24 h. The crude reaction mixture was worked up with aqueous NH_4Cl solution, and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure product **9**{*18,1,1,2*} was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 6-Allyl-3-methyl-4′-nitro-4-(4-nitrobenzyl)-5-prop-2-ynyloxy-biphenyl-2-carboxylate (9{*18,1,1,2*}). Light yellow liquid, yield 92%. IR (neat): ν_{max} 3292 (C≡C-*H*), 2982, 1724 (O−C═O), 1599, 1521, 1444, 1014, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (2H, d, J = 8.4 Hz), 8.14 (2H, d, J = 8.0 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.0 Hz), 5.73−5.69 (1H, m, olefinic-*H*), 4.93 (1H, d, J = 10.0 Hz, olefinic-*H*), 4.69 (1H, d, J = 16.8 Hz, olefinic-*H*), 4.45 (2H, s, $OCH_2C{\equiv}CH$), 4.33 (2H, s, $ArCH_2Ar$), 3.92 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.26 (2H, s, $CH_2CH{=}CH_2$), 2.53 (1H, s, C≡C*H*), 2.21 (3H, s, Ar−CH_3), 0.94 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 168.7 (C, O−C═O), 156.1 (C), 147.3 (C), 146.4 (C), 145.1 (C), 137.8 (C), 136.0 (CH), 133.8 (C), 132.5 (C), 132.0 (C), 130.7 (2 × CH), 129.3 (C), 128.8 (2 × CH), 123.7 (2 × CH), 122.8 (2 × CH), 115.9 (CH_2, CH═CH_2), 78.1 (C, *C*′CH), 76.2 (CH, C≡*C*H), 61.9 (CH_2, $OCH_2C{\equiv}CH$), 61.1 (CH_2, OCH_2CH_3), 33.0 (CH_2), 31.8 (CH_2, $CH_2CH{=}CH_2$), 16.9 (CH_3, Ar-CH_3), 13.7 (CH_3, OCH_2CH_3); LRMS *m*/*z* 515.00 ($M + H^+$), calcd $C_{29}H_{26}N_2O_7$ 514.1740; Anal. Calcd for $C_{29}H_{26}N_2O_7$ (514.17): C, 67.70; H, 5.09; N, 5.44. Found: C, 67.85; H, 5.15; N, 5.61%.

RCM Reactions: Method A. A 10 mL oven-dried round-bottom flask equipped with a stirring bar was charged with diene **9** (0.2 mmol) and Grubbs' first generation catalyst (3.3 mg, 0.004 mmol, 2 mol %) in dry CH_2Cl_2 (4 mL, 0.05 M), and the reaction mixture was stirred under N_2 at room temperature for 3 to 5 h. Solvent CH_2Cl_2 was distilled off at ambient pressure, the crude reaction mixture was directly loaded on silica gel column, and pure RCM products **10** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 8-Methyl-9-(4-nitrobenzyl)-6-(4-nitrophenyl)-2,5-dihydro-benzo[*b*]oxepine-7-carboxylate (10{*18,1,1,1*}). Light yellow liquid, yield 95%. IR (neat): ν_{max} 2918, 1718 (O−C═O), 1643, 1597, 1562, 1520, 1444, 1014, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (2H, d, J = 8.4 Hz), 8.14 (2H, d, J = 8.4 Hz), 7.43 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.4 Hz), 5.68−5.66 (1H, m, olefinic-*H*), 5.40 (1H, d, J = 11.2 Hz, olefinic-*H*), 4.44 (2H, s, $OCH_2CH{=}CH$), 4.25 (2H, s, $ArCH_2Ar$), 3.94 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.19 (2H, br s, $CH_2CH{=}CH$), 2.21 (3H, s, Ar−CH_3), 0.95 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 169.1 (C, O−C═O), 157.5 (C), 147.8 (C), 147.3 (C), 146.5 (C), 145.5 (C), 134.9 (C), 133.4 (C), 133.2 (C), 131.2 (C), 131.1 (C), 130.6 (2 × CH), 129.0 (2 × CH), 127.5 (CH), 125.0 (CH), 123.8 (2 × CH), 123.2 (2 × CH), 70.9 (CH_2, $OCH_2CH{=}CH$), 61.2 (CH_2, OCH_2CH_3), 32.3 (CH_2), 27.0 (CH_2, $CH_2CH{=}CH$), 16.8 (CH_3, Ar-CH_3), 13.7 (CH_3, OCH_2CH_3); LRMS *m*/*z* 489.00 ($M + H^+$), calcd $C_{27}H_{24}N_2O_7$ 488.1584; Anal. Calcd for $C_{27}H_{24}N_2O_7$ (488.15): C, 66.39; H, 4.95; N, 5.73. Found: C, 66.25; H, 4.88; N, 5.81%.

Method B. A 10 mL oven-dried round-bottom flask equipped with a stirring bar was charged with enyne **9**{*18,1,1,2*} (0.2 mmol) and Grubbs' first generation catalyst (8.3 mg, 0.01 mmol, 5 mol %) in dry CH_2Cl_2 (4 mL, 0.05 M), and the reaction mixture was stirred under N_2 at room temperature for 24 h. Solvent CH_2Cl_2 was distilled off at ambient pressure, the crude reaction mixture was directly loaded on silica gel column, and pure RCM product **10**{*18,1,1,2*} was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 8-Methyl-9-(4-nitrobenzyl)-6-(4-nitrophenyl)-3-vinyl-2,5-dihydro-benzo[*b*]oxepine-7-carboxylate (10{*18,1,1,2*}). Light yellow liquid, yield 55%. IR (neat): ν_{max} 2930, 1724 (O−C═O), 1599, 1520, 1452, 1059, 734, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (2H, d, J = 8.4 Hz), 8.17 (2H, d, J = 8.0 Hz), 7.43 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.4 Hz), 6.17 (1H, dd, J = 18.0, 11.2 Hz, olefinic-*H*), 5.76 (1H, br s, olefinic-*H*), 4.90 (1H, d, J = 11.2

Hz, olefinic-*H*), 4.77 (1H, d, J = 18.0 Hz, olefinic-*H*), 4.66 (2H, s, OCH_2), 4.23 (2H, s, ArCH_2Ar), 3.94 (2H, q, J = 6.8 Hz, OCH_2CH$_3$), 3.27 (2H, d, J = 4.8 Hz, CH_2CH=CH), 2.21 (3H, s, Ar−CH_3), 0.95 (3H, t, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 168.9 (C, O−C=O), 157.2 (C), 147.5 (C), 147.3 (C), 146.5 (C), 145.2 (C), 136.9 (CH), 135.9 (C), 134.7 (C), 133.4 (C), 132.6 (C), 131.4 (C), 130.8 (C), 130.5 (2 × CH), 129.0 (2 × CH), 127.1 (CH), 123.8 (2 × CH), 123.2 (2 × CH), 111.3 (CH$_2$, CH=*C*H$_2$), 70.6 (CH$_2$, O*C*H$_2$CH=CH), 61.2 (CH$_2$, O*C*H$_2$CH$_3$), 32.2 (CH$_2$), 26.7 (CH$_2$, *C*H$_2$CH=CH), 16.8 (CH$_3$, Ar-*C*H$_3$), 13.7 (CH$_3$, OCH$_2$*C*H$_3$); LRMS *m*/*z* 513.00 (M − H$^+$), calcd $C_{29}H_{26}N_2O_7$ 514.1740; Anal. Calcd for $C_{29}H_{26}N_2O_7$ (514.17): C, 67.70; H, 5.09; N, 5.44. Found: C, 67.85; H, 5.15; N, 5.56%.

Base-Induced Ring-Opening (BIRO) Reactions. A 10 mL oven-dried round-bottom flask equipped with a stir bar was charged with **10** (0.2 mmol), dry DMSO (4 mL, 0.05 M), to that KO*t*Bu (44.8 mg, 0.4 mmol, 2.0 equiv) was added at 0 °C. The reaction mixture was stirred at 25 °C for 3−4 h. The crude reaction mixture was worked up with water, and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Pure products **11** or **12** [**11**{*18,1,1,2*} is an unstable product at 25 °C and which was rapidly converted into **13**{*18,1,1,2*}] were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 6-Buta-1,3-dienyl-5-hydroxy-3-methyl-4′-nitro-4-(4-nitrobenzoyl)-biphenyl-2-carboxylate (11-{*18,1,1,1*}). Light yellow liquid, yield 75%. IR (neat): ν_{max} 3429 (O-*H*), 2980, 1722 (O−C=O), 1682, 1601, 1525, 1446, 1055, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (2H, d, J = 8.4 Hz), 8.24 (2H, d, J = 8.0 Hz), 8.07 (2H, d, J = 8.4 Hz), 7.41 (2H, d, J = 8.4 Hz), 6.38 (1H, t, J = 10.8 Hz, olefinic-*H*), 6.31−6.21 (1H, m, olefinic-*H*), 5.90 (1H, s, O-*H*), 5.79 (1H, d, J = 10.8 Hz, olefinic-*H*), 5.43 (1H, d, J = 16.4 Hz, olefinic-*H*), 5.36 (1H, d, J = 10.0 Hz, olefinic-*H*), 3.97 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 2.20 (3H, s, Ar−CH_3), 0.95 (3H, t, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 195.0 (C, C=O), 167.9 (C, O−C=O), 150.7 (C), 150.5 (C), 147.4 (C), 145.0 (C), 141.6 (C), 139.7 (C), 136.5 (CH), 134.6 (C), 131.4 (CH), 130.3 (4 × CH), 128.1 (C), 125.8 (C), 124.1 (2 × CH), 123.8 (CH$_2$, CH=*C*H$_2$), 123.2 (2 × CH), 121.8 (CH), 120.5 (C), 61.4 (CH$_2$, O*C*H$_2$CH$_3$), 17.2 (CH$_3$, Ar-*C*H$_3$), 13.7 (CH$_3$, OCH$_2$*C*H$_3$); LRMS *m*/*z* 503.00 (M + H$^+$), calcd $C_{27}H_{22}N_2O_8$ 502.1376; Anal. Calcd for $C_{27}H_{22}N_2O_8$ (502.13): C, 64.54; H, 4.41; N, 5.58. Found: C, 64.71; H, 4.47; N, 5.48%.

[1,7]-Sigmatropic Hydrogen Shift Reactions: Method A. Compounds **11** or **12** (0.1 mmol), DMF (1.0 mL, 0.1 M) were taken in a glass sealed tube, and the mixture was heated at 140 °C under N_2 for 12 to 15 h. Upon cooling to room temperature, the mixture was diluted with dichloromethane (10 mL), washed with NH_4Cl solution (5 mL), and brine (5 mL). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Pure products **13** or **14** were obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 2,7-Dimethyl-8-(4-nitrobenzoyl)-5-(4-nitrophenyl)-2*H*-chromene-6-carboxylate (13{*18,1,1,1*}). Light yellow liquid, yield 65%. IR (neat): ν_{max} 2928, 1724 (O−C=O), 1682, 1599, 1523, 1446, 1008, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (2H, d, J = 8.0 Hz), 8.30 (2H, d, J = 8.0 Hz), 8.08 (2H, d, J = 7.6 Hz), 7.48 (2H, d, J = 8.0 Hz), 5.96 (1H, d, J = 10.0 Hz, olefinic-*H*), 5.63 (1H, dd, J = 10.0, 2.4 Hz, olefinic-*H*), 4.83 (1H, br s, O*CH*), 3.97 (2H, q, J = 6.8 Hz, OCH_2CH$_3$), 2.17 (3H, s, Ar−CH_3), 1.18 (3H, d, J = 6.4 Hz, OCHCH_3), 0.96 (3H, t, J = 6.8 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 194.8 (C, C=O), 168.0 (C, O−C=O), 151.3 (C), 150.6 (C), 147.5 (C), 144.0 (C), 141.5 (C), 136.1 (C), 134.1 (C), 130.6 (2 × CH), 130.2 (2 × CH), 128.0 (CH), 128.0 (C), 127.1 (C), 123.9 (2 × CH), 123.3 (2 × CH), 119.9 (CH), 118.0 (C), 71.8 (CH, O-*C*H), 61.3 (CH$_2$, O*C*H$_2$CH$_3$), 20.9 (CH$_3$), 16.9 (CH$_3$, Ar-*C*H$_3$), 13.7 (CH$_3$, OCH$_2$*C*H$_3$); LRMS *m*/*z* 502.35 (M$^+$), calcd $C_{27}H_{22}N_2O_8$ 502.1376; Anal. Calcd for $C_{27}H_{22}N_2O_8$ (502.13): C, 64.54; H, 4.41; N, 5.58. Found: C, 64.67; H, 4.38; N, 5.65%.

Method B. To the crude compound **11**{*18,1,1,2*}, 5 g of silica (particle size 0.063−0.200 mm), 5 mL of $CHCl_3$ was added, and the reaction mixture stirred at 25 °C for 5.0 h. Pure product **13**{*18,1,1,2*} was obtained by column chromatography (silica gel, mixture of hexane/ethyl acetate).

Data for Ethyl 2,7-Dimethyl-8-(4-nitrobenzoyl)-5-(4-nitrophenyl)-2-vinyl-2*H*-chromene-6-carboxylate (13{*18,1,1,2*}). Light yellow liquid, yield 50%. IR (neat): ν_{max} 3106, 3079, 2982, 1707 (O−C=O), 1684, 1526, 1346, 1233, 1181, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (2H, d, J = 8.8 Hz), 8.31 (2H, d, J = 8.8 Hz), 8.06 (2H, d, J = 8.8 Hz), 7.49 (2H, d, J = 8.8 Hz), 6.02 (1H, d, J = 10.0 Hz, olefinic-*H*), 5.58 (1H, d, J = 10.4 Hz, olefinic-*H*), 5.54 (1H, d, J = 10.4 Hz, olefinic-*H*), 5.09−5.05 (2H, m, olefinic-*H*), 3.98 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 2.17 (3H, s, Ar−CH_3), 1.29 (3H, s, CH_3), 0.96 (3H, t, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT-135): δ 194.9 (C, C=O), 168.1 (C, O−C=O), 150.8 (C), 150.7 (C), 147.6 (C), 144.0 (C), 141.6 (C), 139.1 (CH), 136.1 (C), 134.1 (C), 130.9 (CH), 130.4 (CH), 130.3 (2 × CH), 129.1 (CH), 128.0 (C), 127.3 (C), 123.9 (2 × CH), 123.4 (2 × CH), 119.9 (CH), 117.7 (C), 115.5 (CH$_2$, CH=*C*H$_2$), 78.7 (C), 61.3 (CH$_2$, O*C*H$_2$CH$_3$), 26.8 (CH$_3$), 16.9 (CH$_3$, Ar-*C*H$_3$), 13.8 (CH$_3$, OCH$_2$*C*H$_3$); LRMS *m*/*z* 529.00 (M + H$^+$), calcd $C_{29}H_{24}N_2O_8$ 528.1153; Anal. Calcd for $C_{29}H_{24}N_2O_8$ (528.11): C, 65.90; H, 4.58; N, 5.30. Found: C, 65.78; H, 4.51; N, 5.45%.

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Supporting Information Available. Complete experimental procedures, compound characterization, X-ray crystal structures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis) for all new compounds. Copies of ^{13}C NMR spectrum of all new compounds. Crystallographic

data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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