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α-Alkenoyl Ketene *S*,*S*-Acetal-Based Multicomponent Reaction: An Efficient Approach for the Selective Construction of Polyfunctionalized Cyclohexanones

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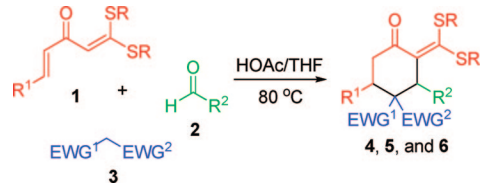

A versatile multicomponent reaction based on the new four-carbon synthons α-alkenoyl ketene *S*,*S*-acetals **1** has been developed. This three-component reaction of readily available α-alkenoyl ketene *S*,*S*-acetals **1** with aldehydes **2** and active methylene compounds **3** proceeds smoothly in acidic medium (glacial acetic acid in tetrahydrofuran) to give various polyfunctionalized cyclohexanones **4**, **5**, and **6** in a highly regio- and diastereoselective manner with good to excellent yields. The reaction can tolerate a broad range of substituents in the three components involved and is proposed to proceed via a tandem Knoevenagel-intermolecular Michael-intramolecular Michael sequence. As an extension of the synthetic application of polyfunctionalized cyclohexanones obtained, unsymmetrical biaryls **7** were synthesized in almost quantitative yields by simple transformations of the corresponding cycloadducts **6**.

Introduction

Multicomponent reactions (MCRs) have been refined in recent years into powerful and useful tools in synthetic chemistry and have attracted increasing attention because complex molecules and drugs can be prepared from cheap and easily available starting materials.[1] In addition, the implementation of several transformations in a single manipulation is highly compatible with the goals of sustainable and "green" chemistry.[2] From this perspective and combined with combinatorial chemistry,[3] the development of versatile MCRs, especially those involving synthons having multiple reactive sites (groups), is particularly desirable.[1] In this paper, we show that α-alkenoyl ketene *S*,*S*-acetals, a kind of 1,4-dien-3-ones[4] bearing a variety of alkenoyl substituents and a ketene dithioacetal subunit that have been successfully used as five-carbon synthons in our previous works,[5] can be taken as new four-carbon synthons in multicomponent reactions.

The utility of functionalized ketene *S*,*S*-acetals **1** (Scheme 1) as versatile intermediates in organic synthesis has been greatly expanded over the past several decades.[5−11] Generally, as 1,3-bielectrophilic three-carbon synthons, α-oxo ketene *S*,*S*-acetals have been widely applied in [3 + 3] annulation reactions for the synthesis of six-membered carbo- (Scheme 1, Strategy 1) and heterocyclic compounds.[6,7] In our research on the chemistry of functionalized ketene *S*,*S*-acetals,[5,8−11] we have taken α-alkenoyl ketene *S*,*S*-acetals as five-carbon 1,5-bielectrophilic double Michael acceptors in the [5 + 1] annulation strategy for

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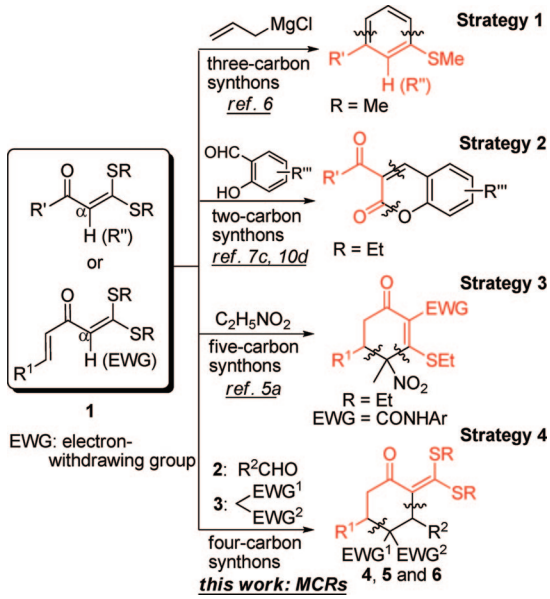
SCHEME 1. Versatile Organic Intermediates: Functionalized Ketene *S*,*S*-Acetals 1

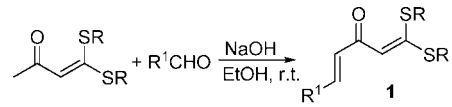


construction of cyclohexenones (Scheme 1, Strategy 3),[5a] dihydropyridones,[5b] and dihydrothiopyranones.[5c] Recently, functionalized ketene *S*,*S*-acetals were also applied as two-carbon dipolar synthons for efficient preparation of coumarins (Scheme 1, Strategy 2)[7c,10d] and the multistep synthesis of polysubstituted furans.[9c] Combining all above synthetic applications of functionalized ketene *S*,*S*-acetals in organic synthesis[5−10] with their potential nucleophilicity of the α-carbon atom,[9c,10] in our present research a cyclization strategy was designed to evaluate the efficiency of the α-alkenoyl ketene *S*,*S*-acetals **1** as four-carbon synthons in MCRs (Scheme 1, Strategy 4). Fortunately, the three-component [4 + 2] cycloaddition reaction of readily available α-alkenoyl ketene *S*,*S*-acetals **1** with the Knoevenagel adducts produced in situ from aldehydes **2** and active methylene compounds **3** was achieved via a tandem Knoevenagel-intermolecular Michael-intramolecular Michael sequence in the presence of glacial acetic acid in tetrahydrofuran to afford polyfunctionalized cyclohexanones **4**, **5**, and **6** in highly regio- and diastereoselective fashion with good to excellent yields. Based on this new strategy, a wide variety of polyfunctionalized cyclohexanones, including extensive changes of SR, R^1, R^2, EWG^1 (EWG = electron-withdrawing group), and EWG^2, were efficiently synthesized in a single step. The results are reported in this paper.

Results and Discussion

Preparation of α-Alkenoyl Ketene *S*,*S*-Acetals 1. According to the procedures described in our previous reports, the selected substrates, α-alkenoyl ketene *S*,*S*-acetals **1a**−**1j** bearing either aromatic or aliphatic R^1 substituents and either acyclic or cyclic dithioacetal groups, were prepared in high to excellent yields by the condensation reaction of the corresponding α-acetyl ketene *S*,*S*-acetals with aldehydes under basic conditions (Scheme 2).[5a−c,9b,11]

SCHEME 2. Preparation of α-Alkenoyl Ketene *S*,*S*-Acetals 1



1a: R^1 = C_6H_5,	R,R = $(CH_2)_2$,	95%
1b: R^1 = 4-$NO_2C_6H_4$,	R,R = $(CH_2)_2$,	90%
1c: R^1 = 4-ClC_6H_4,	R,R = $(CH_2)_2$,	94%
1d: R^1 = 4-$MeOC_6H_4$,	R,R = $(CH_2)_2$,	95%
1e: R^1 = 4-MeC_6H_4,	R,R = $(CH_2)_2$,	93%
1f: R^1 = 3,4-$CH_2O_2C_6H_3$,	R,R = $(CH_2)_2$,	91%
1g: R^1 = 2-furyl,	R,R = $(CH_2)_2$,	90%
1h: R^1 = *t*-Bu,	R,R = $(CH_2)_2$,	70%
1i: R^1 = C_6H_5,	R,R = $(CH_2)_3$,	92%
1j: R^1 = C_6H_5,	R = Et,	81%

Synthesis of Polyfunctionalized Cyclohexanone 4a by the MCR of 1a, 2a, and 3a. On the basis of our previous work, one of the difficulties in studying the MCR of compound **1** with an aldehyde **2** and an active methylene component **3** is to avoid the favorable formation of the 2:1 adducts via sequential C−C coupling of **1** with aldehyde **2** in the presence of Lewis acids (for example, adduct **A** in Table 1).[10a,b,d] The present research started with the model reaction between α-cinnamoyl ketene *S*,*S*-acetal **1a** (1.0 mmol), formaldehyde **2a** (5.0 mmol, 40% aqueous), and dimedone **3a** (1.2 mmol) mediated by simple Brønsted acids (Table 1).[9c] However, extensive experimentation revealed that, similar to the results using Lewis acid catalysis in our previous research,[10a,b,d] the 2:1 adducts **A** together with **B** were isolated, respectively, when hydrochloric acid (2.0 equiv, 36% aqueous) or sulfuric acid (2.0 equiv, 98% aqueous) was selected as the catalyst in THF (4.0 mL) (Table 1, entries 1 and 2). Fortunately, with treatment of the above reaction mixture with glacial acetic acid (2.0 equiv) in THF (4 mL), a cyclization product, the highly substituted cyclohexanone **4a**, was obtained in 57% yield after 24 h of reaction at room temperature in the open air (Table 1, entry 3). Thus, glacial acetic acid was selected to give an acid medium for this selective MCR, and the optimization of the reaction conditions with respect to the amount of acid and the reaction temperature was investigated. The results are described in Table 1. Clearly, a higher temperature accelerated the reaction rate, and cyclohexanone **4a** was obtained in 77% yield within 2.5 h at reflux temperature in the presence of 2.0 equiv of glacial acetic acid in 4.0 mL of THF. The best result was achieved when the reaction proceeded at 80 °C (oil bath temperature) in 2.0 mL of glacial acetic acid and 2.0 mL of THF and with a 1:5:1.2 ratio of **1a**:**2a**:**3a** (Table 1, entry 8).

Possible Mechanism for MCR of 1a, 2a, and 3a. The construction of suitably functionalized (or substituted) six-

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(10) For representative examples of C−C bond-forming reactions at the α-position of functionalized ketene *S*,*S*-acetals, see: (a) Yin, Y.; Wang, M.; Liu, Q.; Hu, J.; Sun, S.; Kang, J. *Tetrahedron Lett.* **2005**, *46*, 4399–4402. (b) Zhang, Q.; Liu, Y.; Wang, M.; Liu, Q.; Hu, J.; Yin, Y. *Synthesis* **2006**, 3009–3014. (c) Yin, Y.; Zhang, Q.; Li, J.; Sun, S.; Liu, Q. *Tetrahedron Lett.* **2006**, *47*, 6071–6074. (d) Yuan, H.-J.; Wang, M.; Liu, Y.-J.; Liu, Q. *Adv. Synth. Catal.* **2009**, *351*, 112–116.

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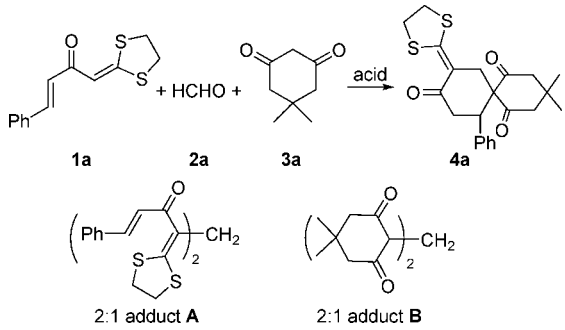
TABLE 1. Optimization of Reaction Conditions of the MCR of 1a, 2a, and 3a[a]



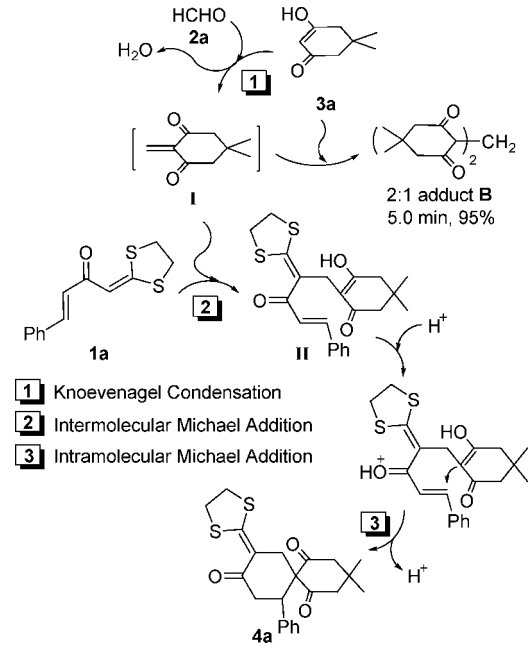
entry	acid	THF (mL)	T (°C)	time	**4a** (%)[b]
1	HCl (2.0 equiv)	4.0	rt	24 h	*c*
2	H_2SO_4 (2.0 equiv)	4.0	rt	24 h	*d*
3	AcOH (2.0 equiv)	4.0	rt	24 h	57
4	AcOH (4.0 equiv)	4.0	rt	24 h	80
5	AcOH (2.0 equiv)	4.0	80	2.5 h	77
6	AcOH (4.0 equiv)	4.0	80	2.5 h	80
7	AcOH (1.0 mL)	3.0	80	1.5 h	85
8	AcOH (2.0 mL)	2.0	80	45 min	93
9	AcOH (3.0 mL)	1.0	80	30 min	90

[a] **1a** (1.0 mmol), **2a** (5.0 mmol, 40% aqueous), **3a** (1.2 mmol). [b] Isolated yield. [c] 2:1 adducts **A** and **B** were isolated in 65% and 90% yields, respectively. [d] 2:1 adducts **A** and **B** were isolated in 60% and 86% yields, respectively.

membered carbocycles is of great interest for the synthesis of natural products and pharmaceutically attractive molecules.[12] Therefore, the development of simple and efficient approaches for the construction of them is desired.[13] Although MCRs have been widely applied for the preparation of a diverse array of polysubstituted heterocyclic compounds,[1] the synthesis of six-membered carbocycles via MCRs are less well developed. In this context, remarkable progresses have been achieved in the four-component cyclization of Fischer carbene complexes, lithium enolates, allylmagnesium bromide with carbon monoxide,[14] and Barbas three-component cycloaddition of 3-buten-2-ones, aldehydes, and active methylene compounds via a domino Knoevenagel/Diels−Alder sequence.[15]

In the present work, the regioselective MCR of α-cinnamoyl ketene *S*,*S*-acetal **1a**, formaldehyde **2a**, and dimedone **3a** leading to cyclohexanone **4a** provides an alternative approach for the construction of six-membered carbocycles. This reaction should be reasonably described as a three-component [4 + 2] cycloaddition. As shown in Scheme 3, the reaction begins with the in situ formation of methylidenedimedone **I** via Knoevenagel condensation of **2a** with **3a**. Then, intermolecular Michael addition of **1a** to **I** produces intermediate **II**, which is protonated and further undergoes an intramolecular Michael addition to generate cyclohexanone **4a**. In our experiments, intermediate **I** could not be isolated from the reaction mixture because of its high reactivity toward nucleophiles.[16] Adduct **B**, which was proved not to react with **1a** under the identical conditions (Table 1, entry 8), was isolated in 95% yield when the Knoevenagel condensation of **2a** (5.0 mmol) with **3a** (1.0 mmol) was performed in glacial acetic acid (2.0 mL) and THF (2.0 mL) at 80 °C (oil bath temperature) for only 5.0 min in the absence of **1a**. The above results suggest that under the optimized reaction conditions, the formations of the 2:1 adducts **A** and **B** (Table 1) can be effectively minimized so that the MCR product **4a** can be constructed through the very reactive intermediate **I** and subsequent conjugate addition with **1a** (Scheme 3).

SCHEME 3. Proposed Mechanism for the MCR of 1a, 2a, and 3a



Scope of the MCRs. With optimized conditions in hand, the scope and limitations of this new MCR were examined in regard to the three components involved. According to the results of the MCRs of **1** with **2a** and **3a** (Table 2), it was found that all selected α-alkenoyl ketene *S*,*S*-acetals **1** bearing aromatic substituents (entries 1−7) reacted efficiently with **2a** and **3a** to give the corresponding cyclohexanones **4** in high yields. In the case of **1h** bearing a bulky aliphatic substituent (*t*-Bu), an acyclic product **IIa**, same as intermediate **II** described in Scheme 2, was obtained (Table 2, entry 8). In addition, both **1i** (with cyclic dithioacetal group) and **1j** (with acyclic dithioacetal group) also allowed the formation of **4h** and **4i** in 77% and 60% isolated yields, respectively (Table 2, entries 9 and 10).

The versatility of the above MCR was further demonstrated with the successful preparation of the corresponding cyclohexanones **5** by treatment of various aldehydes **2** (1.2 mmol) with selected α-alkenoyl ketene *S*,*S*-acetals **1** (1.0 mmol) and dimedone **3a** (1.2 mmol) under the identical conditions as described in Table 1, entry 8. As shown in Table 3, all of the aromatic aldehydes, including benzaldehyde (entries 1−3), aromatic aldehydes bearing either electron-withdrawing (entries

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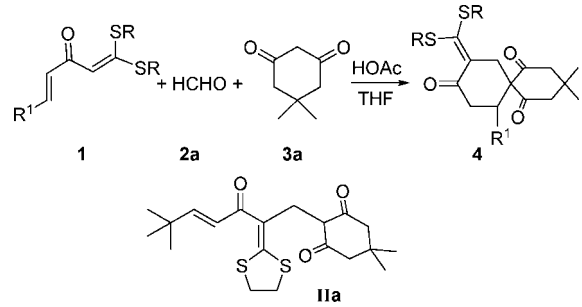
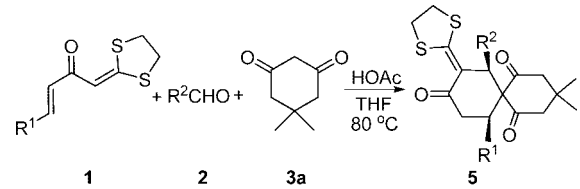
TABLE 2. MCRs for the Synthesis of Cyclohexanones 4: Variation of the α-Alkenoyl Ketene *S*,*S*-Acetals 1[a]



entry	1	R^1	R,R or R	4	time	yield (%)[b]
1	**1a**	C_6H_5	$(CH_2)_2$	**4a**	45 min	93
2	**1b**	4-$NO_2C_6H_5$	$(CH_2)_2$	**4b**	6.0 h	77
3	**1c**	4-ClC_6H_5	$(CH_2)_2$	**4c**	45 min	88
4	**1d**	4-$MeOC_6H_4$	$(CH_2)_2$	**4d**	25 min	91
5	**1e**	4-MeC_6H_4	$(CH_2)_2$	**4e**	35 min	80
6	**1f**	3,4-$CH_2O_2C_6H_3$	$(CH_2)_2$	**4f**	45 min	71
7	**1g**	2-furyl	$(CH_2)_2$	**4g**	15 min	86
8	**1h**	*t*-Bu	$(CH_2)_2$	**IIa**	1.5 h	66
9	**1i**	C_6H_5	$(CH_2)_3$	**4h**	25 min	77
10	**1j**	C_6H_5	Et	**4i**	1.4 h	60

[a] **1** (1.0 mmol), **2a** (5.0 mmol, 40% aqueous), **3a** (1.2 mmol), AcOH (2.0 mL), THF (2.0 mL), 80 °C. [b] Isolated yield.

TABLE 3. MCRs for the Synthesis of Cyclohexanones 5: Variation of Aldehydes 2[a]

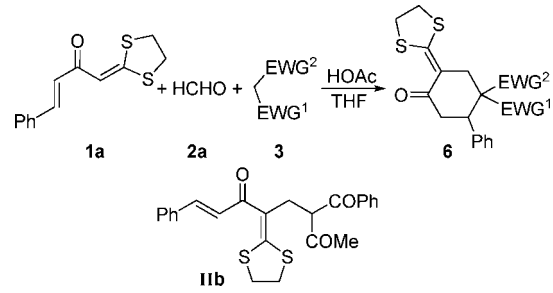


entry	1 R^1	2 R^2	5	time (h)	yield (%)[b]	de (%)[c]
1	**1a** C_6H_5	**2b** C_6H_5	**5a**	4.0	71	99
2	**1c** 4-ClC_6H_4	**2b** C_6H_5	**5b**	8.0	51	81
3	**1d** 4-$MeOC_6H_4$	**2b** C_6H_5	**5c**	4.0	70	92
4	**1a** C_6H_5	**2c** 4-$NO_2C_6H_4$	**5d**	1.0	83	95
5	**1c** 4-ClC_6H_4	**2c** 4-$NO_2C_6H_4$	**5e**	2.0	86	96
6	**1d** 4-$MeOC_6H_4$	**2c** 4-$NO_2C_6H_4$	**5f**	2.0	89	97
7	**1a** C_6H_5	**2d** 4-ClC_6H_4	**5g**	2.5	80	99
8	**1a** C_6H_5	**2e** 4-MeC_6H_4	**5h**	3.0	72	99
9	**1c** 4-ClC_6H_4	**2e** 4-MeC_6H_4	**5i**	3.0	69	84
10	**1d** 4-$MeOC_6H_4$	**2e** 4-MeC_6H_4	**5j**	3.5	78	99
11	**1a** C_6H_5	**2f** 4-$MeOC_6H_4$	**5k**	3.0	60	76
12	**1a** C_6H_5	**2g** 4-pyridyl	**5l**	4.0	70	99
13	**1a** C_6H_5	**2h** *E*-PhCH=CH	**5m**	11.5	50	88
14	**1a** C_6H_5	**2i** Me		24	nr[d]	
15	**1a** C_6H_5	**2j** Cy		24	nr[d]	

[a] **1** (1.0 mmol), **2** (1.2 mmol), **3a** (1.2 mmol), AcOH (2.0 mL), THF (2.0 mL), 80 °C. [b] Isolated yield. [c] Diastereomeric excesses determined by ^{1}H NMR. [d] No reaction.

4−7) or electron-donating substituents (entries 8−11), heteroaromatic aldehyde (entry 12), and unsaturated aldehyde (entry 13), furnished the corresponding cyclohexanones **5** in good to high yields. Interestingly, although formaldehyde **2a** can be successfully applied to this MCR (Table 2), the aliphatic aldehydes, such as acetaldehyde (Table 3, entry 14) and cyclohexanecarbaldehyde (Table 3, entry 15), could not afford the desired product, probably because of their lower reactivity. Nevertheless, it is clear that the above three-component tandem

TABLE 4. MCRs for the Synthesis of Cyclohexanones 6: Variation of Active Methylene Compounds 3[a]



entry	3	EWG^1	EWG^2	6	time	yield(%)[b]
1	**3a**			**6a (≡ 4a)**	45 min	93
2	**3b**			**6b**	40 min	98
3	**3c**			**6c**	1.0 h	60[c]
4	**3d**	MeCO	MeCO	**6d**	24 h	45
5	**3f**	CO_2Et	NO_2	**6e**	16 h	56[d]
6	**3e**	PhCO	MeCO	**IIb**	2.0 h	81
7	**3g**	CO_2Et	MeCO	-	24 h	complex
8	**3h**	CN	CN	-	24 h	-[e]

[a] **1a** (1.0 mmol), **2a** (5.0 mmol, 40% aqueous), **3** (1.2 mmol), AcOH (2.0 mL), THF (2.0 mL), 80 °C. [b] Isolated yield. [c] Performed in a mixture of AcOH (1.0 mL) and THF (3.0 mL) at 80 °C. [d] **6e** was obtained as one diastereoisomer out of the two possible ones. [e] 2:1 adduct **A** was obtained in 61% yield.

reactions provide an efficient and divergent approach to a variety of cyclohexanones **5**.

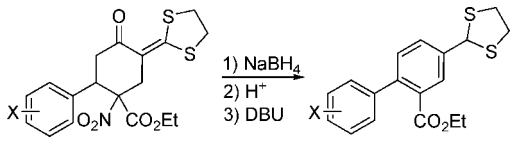
Notably, it was found that the above reactions proceed in a highly diastereoselective manner, giving cyclohexanones **5** in 76−99% de (Table 3, entries 1−13). The major isomer was further determined as the *cis*-isomer by single-crystal X-ray diffraction study of **5e**.[17] This is in accordance with the evidence that the *cis*-isomer of 3,5-diaryl-substituted cyclohexanones is thermodynamically stable.[15b,18]

Next, the reactions of α-cinnamoyl ketene *S*,*S*-acetal **1a** and formaldehyde **2a** with a variety of active methylene compounds **3** were examined (Table 4). As expected, under the optimized conditions as indicated in Table 4, entry 1, cyclopentane-1,3-dione **3b** reacted with **1a** and **2a** to afford the cyclohexanone **6b** in 98% yield within 40 min (Table 4, entry 2). Comparatively, initial treatment of Meldrum's acid **3c** with **1a** and **2a** led to a complex mixture due to probable hydrolysis of Meldrum's acid under acid conditions at elevated temperature. The cycloadduct **6c** could be obtained in good yield by decreasing the amount of acetic acid to 1.0 mL (in 3.0 mL of THF) at reflux temperature (Table 4, entry 3). In the cases of acyclic active methylene components, several features of the MCR are noteworthy. Generally, the reaction rates were slower than those of the cyclic active methylene compounds and the product yields were relatively lower. For instance, cyclohex-

(17) Crystal data for **5e**: $C_{28}H_{26}ClNO_5S_2$, yellow, $M = 556.09$, orthorhombic, space group *Pbca*, $a = 10.9199$ (10), $b = 13.5197$ (2), $c = 40.2340$ (5) Å, $V = 5939.90$ (13) Å^3, $\alpha = 90.00°$, $\beta = 90.00°$, $\gamma = 90.00°$, $Z = 4$, $T = 296$ (2) K, $F_{000} = 3135$, $R_1 = 0.0488$, $wR_2 = 0.1424$.

(18) Rowland, A. T.; Filla, S. A.; Coutlangus, M. L.; Winemiller, M. D.; Chamberlin, M. J.; Czulada, G.; Johnson, S. D.; Sabat, M. *J. Org. Chem.* **1998**, *63*, 4359–4365.

SCHEME 4. Synthesis of Unsymmetrical Biaryls 7 from 6[a]



6 7

entry	6	X	7	total yield of 7
1	**6e**	H	**7a**	99%
2	**6f**[b]	4-MeO	**7b**	98%
3	**6g**[c]	3,4-CH_2O_2	**7c**	95%

[a] Reaction conditions: (1) **4** (1.0 mmol), $NaBH_4$ (0.5 equiv), MeOH (5.0 mL), rt; (2) dilute HCl (0.2 mL, 10% aqueous), THF (5.0 mL), rt; (3) DBU (0.1 mL), DMF (5.0 mL), rt. [b] **6f** was prepared from the MCR of **1d**, **2a**, and **3f** in 51% yield. [c] **6g** was prepared from the MCR of **1f**, **2a**, and **3f** in 53% yield.

anones **6d** and **6e** (Table 4, entries 4 and 5) were obtained in moderate yields from the reaction of acetylacetone **3d** and ethyl nitroacetate **3f** with **1a** and **2a**, respectively, under the above conditions. For benzoylacetone **3e**, the reaction furnished the acyclic cross-coupling product **IIb** within 2.0 h (Table 4, entry 6). Prolonging the reaction time did not give the desired cyclohexanone product. When ethyl acetoacetate **3g** was subjected to the identical conditions, the reaction resulted in a complex mixture (Table 4, entry 7). In the case of malononitrile **3h** as substrate, 2:1 adduct **A** was isolated from the reaction mixture in 61% yield after reacting for 24 h (Table 4, entry 8).

Application of Polyfunctionalized Cyclohexanones in the Synthesis of Unsymmetrical Biaryls. As presented above, we have developed a novel MCR with a broad scope of the three components and provided a practical method for the synthesis of diverse densely functionalized cyclohexanones **4**, **5**, and **6** with an α-oxo ketene *S*,*S*-acetal unit.[5−11] Thus, these cyclohexanones are expected to react with various of 1,3-bielectrophiles for the library synthesis and screening of bio/pharmacologically interesting compounds.[5] As an extension of the synthetic application of polyfunctionalized cyclohexanones obtained above, the synthesis of unsymmetrical biaryls[19] was designed. As shown in Scheme 4, via a sequential reduction of **6e−g** with $NaBH_4$, followed by acid-catalyzed dehydration and elimination of nitrous acid in the presence of DBU,[5a] functionalized unsymmetrical biaryls **7a−c** were produced in almost quantitative yields.

Conclusion

In conclusion, we have developed an efficient multicomponent reaction for the regio- and diastereoselective synthesis of a combinatorial library of polyfounctionalized cyclohexanones. This reaction has several attractive features: the use of α-alkenoyl ketene *S,S*-acetals as new four-carbon synthons in multicomponent reactions, relatively mild reaction conditions, good functional tolerance, good to excellent yields and high regio- and diastereoselectivity in most cases, and potential applications of the polyfunctionalized products. Future studies focused on the development of the MCR are in progress.

Experimental Section

General Procedure for Preparation of 1a−1j (1g as Example).[5a−c,9−11] To a solution of 1-(1,3-dithiolan-2-ylidene)propan-2-one[10a,d,11] (160 mg, 1.0 mmol) and furfural (0.09 mL, 1.1 mmol) in EtOH (5.0 mL) was added NaOH (80 mg, 2.0 mmol) in one portion at room temperature. The reaction mixture was stirred for 2.0 h. After the starting material 1-(1,3-dithiolan-2-ylidene)propan-2-one was consumed as indicated by TLC, the resulting mixture was quenched by ice−water (20 mL) under stirring and neutralized with concentrated hydrochloric acid. The precipitate was collected by filtration, washed with water (20 mL), and dried in vacuo to afford the product (*E*)-1-(1,3-dithiolan-2-ylidene)-4-(furan-2-yl)but-3-en-2-one (**1g**) (205 mg, 90%) as a yellow crystal. Mp 144−146 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (t, J = 6.5 Hz, 2H), 3.46 (t, J = 6.5 Hz, 2H), 6.46−6.47 (dd, J = 2.0, 3.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 6.68 (d, J = 15.5 Hz, 1H), 6.78 (s, 1H), 7.40 (d, J = 15.5 Hz, 1H), 7.47 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 166.5, 151.7, 144.4, 127.9, 124.4, 114.8, 112.4, 112.3, 38.9, 35.4. IR (KBr, cm^{-1}) 3057, 2984, 2928, 1577, 1495. ES-MS *m*/*z* 239.0 [(M + 1)]$^+$. Anal. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.44; H, 4.23. Found: C, 55.69; H, 4.11.

Representative Procedure for the MCRs of 1, 2, and 3. Synthesis of Cyclohexanones 4 and 6 (Reaction of 1a, 2a, and 3a as Example). To a solution of **1a** (248 mg, 1.0 mmol), **2a** (0.37 mL, 5.0 mmol, 40% aqueous), and **3a** (168 mg, 1.2 mmol) in THF (2.0 mL) was added AcOH (2.0 mL) at 80 °C. The mixture was stirred for 45 min at 80 °C and then quenched with water (50 mL). The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ether 3/1, v/v) to give **4a** (372 mg, 93%) as a light yellow crystal.

Synthesis of Cyclohexanones 5 (Reaction of 1c, 2c, and 3a As example). To a solution of **1c** (282 mg, 1.0 mmol), **2c** (181 mg, 1.2 mmol), and **3a** (168 mg, 1.2 mmol) in THF (2.0 mL) was added AcOH (2.0 mL) at 80 °C. The mixture was stirred for 2.0 h at 80 °C and then quenched with water (50 mL). The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ether 3/1, v/v) to give a mixture of *cis*- and *trans*-isomers **5e** (505 mg, 91%, de, 96%). Recrystallization of the isomer mixture in acetone/petroleum ether (1/2, v/v) afforded *cis*-isomer **5e** (478 mg, 86%) as a yellow crystal.

10-(1,3-Dithiolan-2-ylidene)-3,3-dimethyl-7-phenylspiro[5.5]-undecane-1,5,9-trione (4a). Mp 224−226 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 3H), 0.88 (s, 3H), 1.95 (d, J = 16.0 Hz, 1H), 2.37 (d, J = 16.0 Hz, 1H), 2.40−2.45 (m, 2H), 2.60 (dd, J = 5.0, 18.0 Hz, 1H), 2.80 (d, J = 16.0 Hz, 1H), 2.97 (dd, J = 10.0, 18.0 Hz, 1H), 3.11 (d, J = 16.0 Hz, 1H), 3.36−3.44 (m, 4H), 3.70 (dd, J = 5.0, 10.0 Hz, 1H), 7.04 (d, J = 7.5 Hz, 2H), 7.26−7.30 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 209.0, 191.4, 160.6, 138.5, 128.8 (2C), 128.4 (2C), 128.1, 118.3, 66.8, 54.3, 53.0, 47.4, 39.9, 39.4, 36.1, 35.0, 30.1, 30.0, 27.7. IR (KBr, cm^{-1}) 3035, 2954, 1723, 1694, 1617, 1459. ES-MS *m*/*z* 401.0 [(M + 1)]$^+$. Anal. Calcd for $C_{22}H_{24}O_3S_2$: C, 65.97; H, 6.04. Found: C, 65.68; H, 6.11.

11-(4-Chlorophenyl)-8-(1,3-dithiolan-2-ylidene)-3,3-dimethyl-7-(4-nitrophenyl)spiro[5.5]undecane-1,5,9-trione (5e). Mp 188−190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.23 (s, 3H), 0.57 (s, 3H), 0.99 (d, J = 16.5 Hz, 1H), 2.07 (d, J = 16.5 Hz, 1H), 2.18 (t, J = 19.0 Hz, 2H), 2.56 (d, J = 18.5 Hz, 1H), 3.00−3.07 (m, 2H), 3.15−3.24 (m, 3H), 3.62 (d, J = 12.0 Hz, 1H), 5.33 (s, 1H), 7.04 (d, J = 8.0 Hz, 2H), 7.33−7.36 (m, 4H), 8.00 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 208.3, 192.3, 162.5, 147.1, 146.4, 135.6, 134.5 (2C), 133.4, 130.1 (3C), 129.1, 123.1, 122.8 (2C), 72.9, 55.4, 53.8, 51.8, 48.3, 38.6, 38.1, 37.1, 31.0, 29.1, 26.1. IR (KBr, cm^{-1}) 3028, 2954, 1683, 1512, 1491, 1346. ES-MS *m*/*z* 556.0 [(M + 1)]$^+$. Anal. Calcd for $C_{28}H_{26}ClNO_5S_2$: C, 60.48; H, 4.71; N, 2.52. Found: C, 60.61; H, 4.82; N, 2.55.

(19) (a) Bringmann, G.; Gunther, C.; Schupp, O.; Tesler, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer-Verlag: New York, 2001; Vol. 81, pp 1−293. (b) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022–10025.

Typical Procedure for the Transformation of 6 to 7 (7a as Example). A mixture solution of **6e** (393 mg, 1.0 mmol) and $NaBH_4$ (19 mg, 0.5 mmol) in MeOH (5.0 mL) was stirred for 20 min at room temperature and then quenched with water (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was concentrated in vacuo to yield a yellow oil which was redissolved in THF (5.0 mL) and treated with dilute hydrochloric acid (0.2 mL, 10% aqueous) for 20 min at room temperature. Then, this mixture was diluted with 20 mL of water and neutralized with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (3 × 15 mL) and sequential removing of CH_2Cl_2 in *vacuo*, the yellow residual oil was obtained and further treated with DBU (0.1 mL) in DMF (5.0 mL) for 30 min at room temperature. The resulting mixture was diluted with water (50 mL), neutralized with dilute hydrochloric acid and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with water (30 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to give ethyl 4-(1,3-dithiolan-2-yl)biphenyl-2-carboxylate (**7a**) (326 mg, 99%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.0 Hz, 3H), 3.37−3.42 (m, 2H), 3.51−3.56 (m, 2H), 4.07 (q, J = 7.0 Hz, 2H), 5.69 (s, 1H), 7.28−7.40 (m, 6H), 7.69−7.71 (m, 1H), 7.94 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 142.1, 141.0, 140.0, 131.3, 130.9, 130.6, 129.3, 128.3 (2C), 128.0 (2C), 127.2, 61.0, 55.4, 40.4 (2C), 13.6. IR (KBr, cm^{-1}): 3058, 2993, 1708, 1516, 1292. ES-MS: m/z 331.0 $[(M + 1)]^+$. Anal. Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49; Found: C, 65.21; H, 5.58.

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Supporting Information Available: Experimental details; spectral and analytical data for compounds **4**, **5**, **6**, **7**, and **II**; copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds; and crystallographic data for **5e** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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