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Unexpected synthesis of 1,3,5-triarly-1,5-diketones from aryl ketones via di-enamine mechanism

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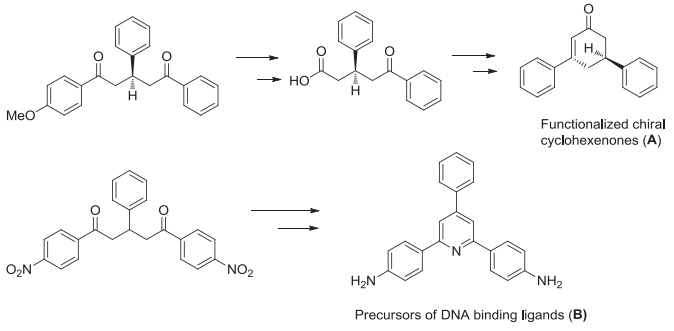
ABSTRACT

An unexpected reaction of aryl ketone with acetohydrazone of aromatic aldehyde via 1,2-di-enamine/di-iminium mechanism was discovered, leading to efficient synthesis of 1,3,5-triaryl-1,5-diketones in good to excellent yields.

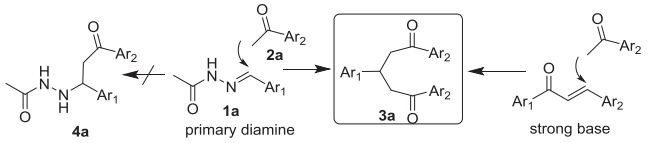
1. Introduction

1,5-Diketones are extremely important synthetic intermediates and desirable starting materials for generating many heterocyclic and polyfunctional compounds.[1,2] Such as, the functionalized chiral cyclohexenones (**A**)[1d] and 2,4,6-triarylpyridine (**B**) as precursors of DNA binding ligands[2d] were all obtained from the corresponding 1,3,5-triaryl-1,5-diketones (Scheme 1).



Scheme 1. Application of 1,5-diketones.

Michael addition is one of the most efficacious methods for the synthesis of this kind of compounds.[3] Even though, there have been few reports on the preparation of 1,3,5-triphenyl-1,5-dikeones through the Michael addition of aryl ketones to chalcones,[4] due to the low reactivity and high steric hindrance for both substrates. Moreover, the harsh reaction conditions, such as the use of excessive strong base, always led to the lower yields and the limited substrate scope. Thus it is challenging and highly desirable to develop a mild efficient strategy for the preparation of this kind of compounds. We disclose here an unexpected transformation of aryl ketones for the synthesis of 1,3,5-triphenylpentane-1,5-dione derivatives catalyzed by 1,2-primary diamine via a synergetic di-enamine mechanism (Scheme 2).



Scheme 2. Unexpected synthesis of 1,5-diketones from aryl ketones.

The Mannich type reactions of acetohydrazone of aromatic aldehyde **1a** and aryl ketones **2a** were initially designed (Scheme 2), based on recent papers[5] and our discovery that 1,2-primary amine catalysts could efficiently activate chalcones[6a,b] furanones[6c] and aryl ketones[6d] (Scheme 3). The model reaction of **1a** and **2a** was

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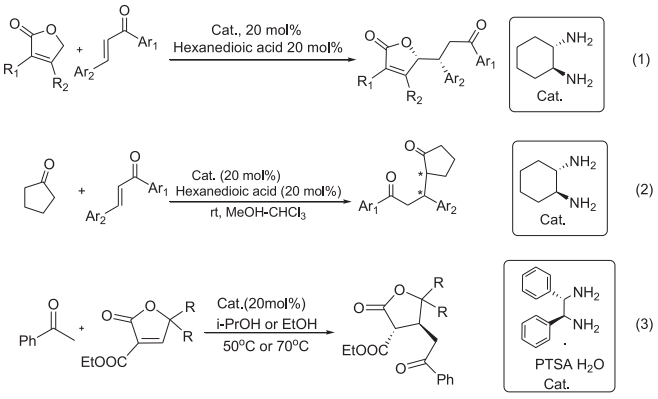
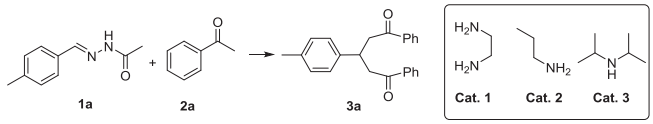


Scheme 3. Efficient 1,2-diamine catalyzed reactions of ketones.

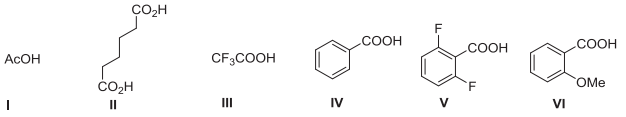
first carried out using our reported method[6b] at room temperature in MeOH with ethylenediamine–HOAc (1:2) as the catalyst. However, no desired product **4a** was observed in the reaction, and much to our surprise product **3a** was separated in about 12% yield (Table 1, entry 1). The interesting discovery encouraged us to further develop this reaction into an efficient method for the synthesis of 1,3,5-triphenyl-1,5-dikeones.

Table 1
Optimization of the reaction conditions[a]



Entry	Solvent	Catalyst	Additives I–VI	Yield (**3a**) (%)
1	MeOH	1	I	12
2	DCM	1	I	Trace
3	Toluene	1	I	n.r.
4	THF	1	I	n.r.
5	EtOH	1	I	10
6	MeOH	2	I	n.r.
7	MeOH	3	I	n.r.
8	MeOH	1	I	20
9	MeOH	1+TEA	I	64
10	MeOH	TEA	I	n.r.
11	MeOH	1+TEA	II	67
12	MeOH	1+TEA	III	39
13	MeOH	1+TEA	IV	60
14	MeOH	1+TEA	V	73
15	MeOH	1+TEA	VI	72

Additives I–VI.



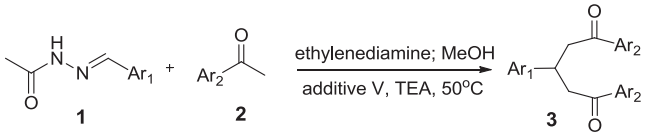
[a] Entries 1–5: the loading of catalyst was 30 mol %; Entries 6–15: the loading of catalyst was 100 mol % and reactions were carried out at 50 °C.

2. Result and discussion

To improve the yield, the model reaction was tested in different solvents, and the effect of different solvents on this reaction revealed that the reaction could only proceed in protic polar solvents such as MeOH/EtOH (Table 1, entries 1 and 5), which is consistent with our previous discovery.[6] Then the catalytic efficiency of different catalysts was examined in MeOH with additive **I** (Table 1, entries 1, 6 and 7). Interestingly, simple primary amine (entry 6, cat. 2) and secondary amine (entry 7, cat. 3) did not show any catalytic effect. Only 1,2-primary diamine (entry 1, cat. 1) could catalyze the reaction, indicating the synergetic catalytic mechanism. Subsequently, the reaction was further explored in MeOH with ethylenediamine as the catalyst. The yield of **3a** was slightly improved to 20% with 100% loading of catalyst at 50 °C (entry 8). Inspired by our previous discovery[7] that TEA might improve the catalytic efficiency in the enamine/iminum mechanism, 1 equiv of TEA was added in the system, and we were delight to find that the yield of **3a** was significantly improved to 64% (entry 9). Moreover, the reaction did not proceed in the absence of ethylenediamine (entry 10), which could confirm the catalytic action of ethylenediamine. Subsequently, the acid additive was further examined as well, and interestingly, mostly reported strong acid CF_3COOH (**III**) did not work well in this case. The benzoic acids **V** and **VI** turned out to be the best additives.

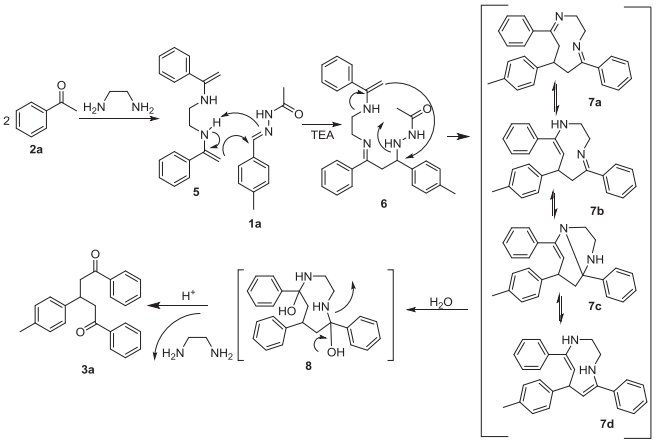
With the optimized reaction conditions, the structural diversity of the substrates in this reaction was examined. As shown in Table 2, most of the reactions gave the desired products **3** in good to excellent yields with this catalytic system. The electronic property and position of the substituents on the aromatic ring of substrates **1** do not significantly influence the reaction, except for the strong electron-donating group (–MeO, entry 5) and strong electron-withdrawing group ($-CO_2Me$, entry 6). Even the acetohydrazone from cinnamaldehyde (**1k**) could still be efficiently transformed into **3k** in 86% yield (Table 2, entry 11). On the contrary, the electronic property of substituents on aryl ketones **2** showed apparent effect in the reaction. This further implied that aryl ketones might be activated via enamine mechanism to function as Mannich donors. From the results of entries 14–17 and 19–21, we can see that mild electronic property of the substituents on the aromatic ring of aryl ketones **2** could improve the synthesis of **3** to excellent yield (Table 2, entry 21, 94% yield). However the strong electron withdrawing or electron donating groups on the aryl ring of aryl ketones **2** are unfavorable for the reactions (Table 2, entries 17 and 19). Moreover, this method is also suitable for the heterocyclic substrates (Table 2, entries 12, 13 and 18).

Table 2
Substrate scope of 1,2-diamine catalyzed reaction between aryl methyl ketones and *N*-acetyl aromatic aldehyde hydrazone

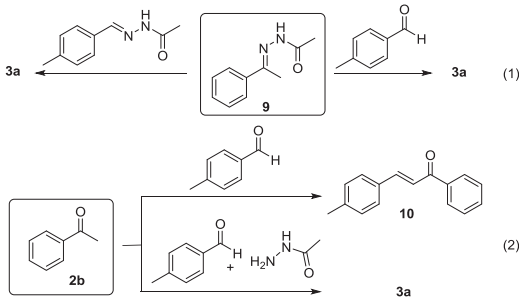


Entry	Ar_1	Ar_2	Yield (%)
1	4-MePh	Ph	73(**3a**)
2	Ph	Ph	89(**3b**)
3	4-ClPh	Ph	80(**3c**)
4	4-FPh	Ph	84(**3d**)
5	4-MeOPh	Ph	68(**3e**)
6	4-CO_2MePh	Ph	45(**3f**)
7	2-BrPh	Ph	81(**3g**)
8	3-ClPh	Ph	83(**3h**)
9	3,4-(OCH_2O)Ph	Ph	70(3i)
10	3,4-dichloro	Ph	81(**3j**)
11	PhCH=CH	Ph	86(**3k**)
12	3-Indole	Ph	62(**3l**)
13	2-Pyrrole	Ph	54(**3m**)
14	4-MePh	4-FPh	80(**3n**)
15	4-MePh	4-BrPh	61(**3o**)
16	4-MePh	4-MeOPh	54(**3p**)
17	4-MePh	4-NO_2Ph	54(**3q**)
18	4-MePh	2-Thiophene	66(**3r**)
19	4-ClPh	4-MeOPh	52(**3s**)
20	4-ClPh	4-BrPh	77(**3t**)
21	4-ClPh	4-MePh	94(**3u**)

The novel mechanism was proposed based on the fact that the interesting direct transformation of aryl ketones could only be catalyzed by 1,2-primary diamine (Scheme 4). The aryl ketones might be activated via di-enamine intermediate **5**, which further reacted with **1a** to form **6**, and the transformation of **6** to **7** might be a synergetic process.[8] Fortunately, the key intermediate **7c** was separated and characterized by ^{1}H NMR and Mass spectra (MW 366.67), which was found to be easily converted to **3a** catalyzed by acid (See Supplementary data). Furthermore, acetohydrazone of aryl ketone **9** could not react with substrate **1a** and aromatic aldehyde under the same catalytic conditions, further confirming the enamine activation of aryl ketones (Scheme 5, (1)). The reaction of aryl ketone and aryl aldehyde led to chalcone **10** instead of **3a** (Scheme 5, (2)), which ruled out the chalcone pathway. This also tells us that the cleavage of the acetylhydrazide in **6** to **7** might also proceed via a synergetic pathway. The preformed acetylhydrazone **1a** is also essential in this reaction, because the three component reaction of aryl acetone **2a**, 4-methylbenzaldehyde and acetohydrazide could not be catalyzed to afford **3a** (Scheme 5, (2)).



Scheme 4. Proposed synergistic mechanism.



Scheme 5. Further verified experiments for the proposed synergistic mechanism.

3. Conclusion

In summary, an interesting reaction of aryl ketone and acetohydrazone catalyzed by 1,2-primary diamine was discovered. After careful optimization of the reaction conditions, it was found to be an efficient method for the synthesis of 1,3,5-triaryl-1,5-diketones directly from aryl ketones. Importantly, the mild reaction conditions allow the synthesis of a variety of 1,3,5-triaryl-1,5-diketones from a wide range of substrates. The novel synergetic mechanism was rationally proposed and confirmed by the capture of key intermediate **7**. We anticipate that this novel and mild reaction of aryl ketones could be further employed in achieving biologically important molecules in organic chemistry and medicinal chemistry in the future.

4. Experimental section

4.1. General information

All chemicals were purchased from commercial sources without further purification. All of the reactions were monitored by thin layer chromatography (TLC) on GF_{254} silica gel plates. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 (400 MHz) spectrometer in needful D-reagents with tetramethylsilane (TMS) as an internal reference. NMR chemical shifts are reported as values (parts per million) relative to internal tetramethylsilane and splitting patterns are designated as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. HRMS of additional products were carried out on Brucker Apex IV FTMS. Melting points were measured on X5A made by Beijing Fukai Company, China.

4.2. General procedure of the synthesis of the products 3

A mixture of *p*-tolualdehyde (0.5 mmol), acethydrazine (0.5 mmol) in CH_3OH (5 mL) was stirred at 50 °C for 4 h (1 was formed). Then 1,2-diamine (0.5 mmol), 2,6-difluorobenzoic acids (1 mmol), TEA (0.5 mmol) and acetophenone (**2**, 2 mmol) were added and the reaction was continued for another 72 h. After cooling, AcOH (2 mL) was added and the resulting mixture was allowed to stir at room temperature for 4 h. The solvent was evaporated under vacuum and the residue was diluted with EtOAc (15 mL), and washed with brine, dried over anhydrous Na_2SO_4, and concentrated at reduced pressure. The crude product was further purified by column chromatography on silica gel (PE–EtOAc=20:1) to get the final product **3**.

*4.2.1. 1,5-Diphenyl-3-(p-tolyl)pentane-1,5-dione (**3a**).* White solid; yield 73%, mp: 99.9–101.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J=7.4 Hz, 4H), 7.53 (t, J=7.4 Hz, 2H), 7.43 (t, J=7.6 Hz, 4H), 7.16 (d, J=7.9 Hz, 2H), 7.07 (d, J=7.9 Hz, 2H), 4.14–3.94 (m, 1H), 3.47 (dd, J=16.6, 7.0 Hz, 2H), 3.32 (dd, J=16.6, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 140.8, 137.0, 136.2, 133.1, 129.3, 128.6, 128.2, 127.3, 45.1, 36.9, 21.0; HRMS calcd for $C_{24}H_{23}O_2^+$ $[M+H]^+$ 343.1706, found: 343.1693.

*4.2.2. 1,3,5-Triphenylpentane-1,5-dione (**3b**).* Pale solid; yield 89%, mp: 97.1–98.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.91 (m, 4H), 7.60–7.52 (m, 2H), 7.49–7.40 (m, 5H), 7.27 (dd, J=6.7, 4.0 Hz, 4H), 4.06 (dd, J=14.0, 7.0 Hz, 1H), 3.50 (dd, J=16.6, 7.0 Hz, 2H), 3.36 (dd, J=16.6, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 143.8, 136.9, 133.1, 128.6, 128.2, 127.5, 126.7, 112.2, 44.9, 37.3; HRMS calcd. For $C_{23}H_{21}O_2^+$ $[M+H]^+$ 329.1541, found: 329.1536.

*4.2.3. 3-(4-Chlorophenyl)-1,5-diphenylpentane-1,5-dione (**3c**).* White solid; yield 80%, mp: 93.8–94.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J=5.2, 3.3 Hz, 4H), 7.51 (m, 6H), 7.23 (m, 4H), 4.05 (dd, J=14.0, 7.0 Hz, 1H), 3.49 (dd, J=16.8, 6.8 Hz, 2H), 3.33 (dd, J=16.8, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 142.3, 136.8, 133.2, 132.4, 128.9, 128.7, 128.6, 128.1, 44.7, 36.6; HRMS calcd for $C_{23}H_{20}ClO_2^+$ $[M+H]^+$ 363.1145, found: 363.1146.

*4.2.4. 3-(4-Fluorophenyl)-1,5-diphenylpentane-1,5-dione (**3d**).* Pale yellow solid; yield 84%, mp: 66.3–67.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J=5.2, 3.3 Hz, 4H), 7.55 (ddd, J=6.8, 4.0, 1.2 Hz, 2H), 7.44 (dd, J=10.5, 4.7 Hz, 4H), 7.31–7.19 (m, 1H), 7.04–6.88 (m, 3H), 4.07 (p, J=7.0 Hz, 1H), 3.49 (dd, J=16.7, 6.8 Hz, 2H), 3.32 (dd, J=16.7, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 139.4, 136.8, 133.2, 129.0, 129.0, 128.7, 128.2, 115.5, 115.3, 112.4, 112.2, 45.0, 36.6; HRMS calcd. For $C_{23}H_{20}FO_2^+$ $[M+H]^+$ 347.1446, found: 347.1442.

*4.2.5. 3-(4-Methoxyphenyl)-1,5-diphenylpentane-1,5-dione (**3e**).* White solid; yield 68%, mp: 70.9–71.7 °C. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.02–7.86 (m, 4H), 7.60–7.49 (m, 2H), 7.43 (dd, *J*=10.5, 4.7 Hz, 4H), 7.19 (d, *J*=8.7 Hz, 2H), 6.80 (d, *J*=8.7 Hz, 2H), 4.02 (p, *J*=7.0 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, *J*=16.5, 6.9 Hz, 2H), 3.31 (dd, *J*=16.5, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 158.2, 137.0, 135.8, 133.1, 128.6, 128.4, 128.2, 114.0, 55.2, 45.2, 36.6; HRMS calcd for $C_{24}H_{23}O_3^+$ $[M+H]^+$ 359.1640, found: 359.1642.

*4.2.6. Methyl 4-(1,5-dioxo-1,5-diphenylpentan-3-yl)benzoate (**3f**).* Pale yellow solid; yield 45%, mp: 95.7–96.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00–7.87 (m, 6H), 7.55 (dd, *J*=10.5, 4.3 Hz, 2H), 7.45 (t, *J*=7.6 Hz, 4H), 7.37 (d, *J*=8.3 Hz, 2H), 4.14 (p, *J*=7.0 Hz, 1H), 3.88 (s, 3H), 3.52 (dd, *J*=16.9, 6.8 Hz, 2H), 3.37 (dd, *J*=17.0, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 166.9, 149.3, 136.8, 133.3, 130.0, 128.7, 128.6, 128.1, 127.6, 52.0, 44.5, 37.0; HRMS calcd. For $C_{25}H_{23}O_4^+$ $[M+H]^+$ 387.1590, found: 387.1591.

*4.2.7. 3-(2-Bromophenyl)-1,5-diphenylpentane-1,5-dione (**3g**).* White solid; yield 81%, mp: 87.0–89.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.94 (m, 4H), 7.55 (ddt, *J*=6.7, 3.4, 1.2 Hz, 3H), 7.44 (dd, *J*=10.5, 4.7 Hz, 4H), 7.33 (dd, *J*=7.8, 1.6 Hz, 1H), 7.30–7.19 (m, 1H), 7.04 (td, *J*=7.9, 1.7 Hz, 1H), 4.53 (p, *J*=7.0 Hz, 1H), 3.53 (dd, *J*=16.9, 7.2 Hz, 2H), 3.44 (dd, *J*=16.9, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 142.5, 136.8, 133.4, 133.2, 128.6, 128.2, 128.2, 128.1, 127.7, 124.5, 43.2, 36.3; HRMS calcd. For C23H20BrO2$^+$ $[M+H]^+$ 407.0644, found: 407.0641.

*4.2.8. 3-(3-Chlorophenyl)-1,5-diphenylpentane-1,5-dione (**3h**).* Yellow solid; yield 83%, mp: 92.3–94.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.87 (m, 4H), 7.55 (t, *J*=7.4 Hz, 2H), 7.44 (t, *J*=7.6 Hz, 4H), 7.28 (s, 1H), 7.20 (d, *J*=5.2 Hz, 2H), 7.15 (ddd, *J*=9.2, 4.2, 2.0 Hz, 1H), 4.06 (p, *J*=7.0 Hz, 1H), 3.49 (dd, *J*=16.9, 6.8 Hz, 2H), 3.34 (dd, *J*=16.9, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 146.0, 136.7, 134.3, 133.3, 129.9, 128.7, 128.2, 127.6, 126.9, 126.0, 44.6, 36.7; HRMS calcd. For $C_{23}H_{20}ClO_2^+$ $[M+H]^+$ 363.1145, found: 363.1148.

*4.2.9. 3-(Benzo[d][1,3]dioxol-5-yl)-1,5-diphenylpentane-1,5-dione (**3i**).* Red solid; yield 70%, mp: 87.3–87.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04–7.81 (m, 4H), 7.61–7.50 (m, 2H), 7.44 (t, *J*=7.6 Hz, 4H), 6.84–6.63 (m, 3H), 5.88 (s, 2H), 3.99 (p, *J*=7.0 Hz, 1H), 3.44 (dd, *J*=16.6, 6.9 Hz, 2H), 3.29 (dd, *J*=16.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 147.7, 146.2, 137.7, 136.9, 133.1, 128.6, 128.2, 120.5, 108.3, 107.9, 100.9, 45.2, 37.1; HRMS calcd for $C_{24}H_{21}O_4^+$ $[M+H]^+$ 373.1431, found: 373.1434.

*4.2.10. 3-(3,4-Dichlorophenyl)-1,5-diphenylpentane-1,5-dione (**3j**).* White solid; yield 81%, mp: 108.1–108.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.89 (m, 4H), 7.63–7.52 (m, 2H), 7.44 (dd, *J*=10.6, 4.7 Hz, 4H), 7.36 (d, *J*=2.2 Hz, 1H), 7.29 (d, *J*=8.4 Hz, 1H), 7.17 (dd, *J*=8.4, 2.2 Hz, 1H), 4.49 (p, *J*=6.9 Hz, 1H), 3.53 (dd, *J*=17.0, 7.0 Hz, 2H), 3.43 (dd, *J*=17.0, 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 139.5, 136.7, 134.4, 133.3, 132.8, 129.8, 129.4, 128.7, 128.1, 127.3, 42.8, 33.5; HRMS calcd for $C_{23}H_{19}Cl_2O_2^+$ $[M+H]^+$ 397.0762, found: 397.0757.

*4.2.11. 1,5-Diphenyl-3-styrylpentane-1,5-dione (**3k**).* Pale yellow solid; yield 86%, mp: 58.6–59.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06–7.96 (m, 4H), 7.61–7.52 (m, 2H), 7.46 (dd, *J*=10.5, 4.7 Hz, 4H), 7.33–7.24 (m, 4H), 7.21–7.15 (m, 1H), 6.43 (d, *J*=15.9 Hz, 1H), 6.29 (dd, *J*=15.9, 8.1 Hz, 1H), 3.74–3.55 (m, 1H), 3.36 (dd, *J*=16.5, 6.5 Hz, 2H), 3.20 (dd, *J*=16.5, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 137.1, 137.0, 133.1, 131.9, 130.5, 128.7, 128.5, 128.2, 127.3, 126.3, 43.4, 35.1; HRMS calcd for $C_{25}H_{23}O_2^+$ $[M+H]^+$ 355.1699, found: 355.1693.

*4.2.12. 3-(1H-Indol-3-yl)-1,5-diphenylpentane-1,5-dione (**3l**).* Red solid; yield 62%, mp: 106.3–107.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (Br, 1H), 7.99–7.92 (m, 4H), 7.63 (d, *J*=7.9 Hz, 1H), 7.52 (t, *J*=7.4 Hz, 2H), 7.42 (t, *J*=7.6 Hz, 4H), 7.31 (d, *J*=8.1 Hz, 1H), 7.20–7.12 (m, 1H), 7.12–7.04 (m, 2H), 4.40 (p, *J*=6.9 Hz, 1H), 3.62 (dd, *J*=16.5, 7.0 Hz, 2H), 3.49 (dd, *J*=16.5, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 137.0, 136.5, 133.0, 128.6, 128.2, 126.2, 122.0, 121.8, 119.4, 119.0, 118.2, 111.4, 44.3, 29.1; HRMS calcd. For $C_{25}H_{22}NO_2^+$ $[M+H]^+$ 368.1646, found: 368.1645.

*4.2.13. 1,5-Diphenyl-3-(1H-pyrrol-2-yl)pentane-1,5-dione (**3m**).* Yellow solid; yield 54%, mp: 41.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.92 (m, 4H), 7.56 (t, *J*=7.4 Hz, 2H), 7.45 (t, *J*=7.6 Hz, 5H), 6.68 (dd, *J*=4.1, 2.6 Hz, 1H), 6.09 (dd, *J*=5.8, 2.8 Hz, 1H), 5.98 (br, 1H), 4.15 (p, *J*=6.5 Hz, 1H), 3.50 (d, *J*=6.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 136.8, 135.0, 133.4, 128.7, 128.1, 116.9, 107.6, 103.8, 43.7, 28.9; HRMS calcd. For $C_{21}H_{20}NO_2^+$ $[M+H]^+$ 318.1484, found: 318.1489.

*4.2.14. 1,5-Bis(4-fluorophenyl)-3-(p-tolyl)pentane-1,5-dione (**3n**).* Colorless oil; yield 80%, ^1H NMR (400 MHz, $CDCl_3$) δ 8.07–7.95 (m, 4H), 7.15–7.05 (m, 8H), 3.98 (p, *J*=7.0 Hz, 1H), 3.45 (dd, *J*=16.5, 7.0 Hz, 2H), 3.28 (dd, *J*=16.5, 7.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 167.0, 164.5, 140.4, 136.4, 133.3, 133.3, 130.9, 130.8, 129.4, 127.2, 115.8, 115.6, 44.9, 37.0, 21.0; HRMS calcd. For $C_{24}H_{21}F_2O_2^+$ $[M+H]^+$ 379.1510, found: 379.1504.

*4.2.15. 1,5-Bis(4-bromophenyl)-3-(p-tolyl)pentane-1,5-dione (**3o**).* White solid; yield 61%, mp: 145.7–146.2 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 4H), 7.59–7.53 (m, 4H), 7.10 (dd, *J*=23.3, 8.1 Hz, 4H), 3.97 (t, *J*=7.0 Hz, 1H), 3.43 (dd, *J*=16.6, 7.0 Hz, 2H), 3.26 (dd, *J*=16.6, 7.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 140.3, 136.5, 135.6, 131.9, 129.7, 129.4, 128.3, 127.2, 44.9, 36.8, 21.0; HRMS calcd. For C24H21Br2O2$^+$ $[M+H]^+$ 498.9913, found: 498.9903.

*4.2.16. 1,5-Bis(4-methoxyphenyl)-3-(p-tolyl)pentane-1,5-dione (**3p**).* Colorless oil; yield 54%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.86 (m, 4H), 7.15 (d, *J*=8.1 Hz, 2H), 7.07 (d, *J*=7.9 Hz, 2H), 6.99–6.83 (m, 4H), 4.06–3.93 (m, 1H), 3.84 (s, 6H), 3.41 (dd, *J*=16.2, 7.0 Hz, 2H), 3.24 (dd, *J*=16.2, 7.1 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 163.4, 141.0, 136.1, 130.5, 130.1, 129.3, 127.3, 113.7, 55.5, 44.9, 37.4, 21.0; HRMS calcd. For $C_{26}H_{27}O_4^+$ $[M+H]^+$ 403.1899, found: 403.1904.

*4.2.17. 1,5-Bis(4-nitrophenyl)-3-(p-tolyl)pentane-1,5-dione (**3q**).* Orange solid; yield 54%, mp: 128.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35–8.24 (m, 4H), 8.15–8.00 (m, 4H), 7.12 (dd, *J*=19.8, 8.1 Hz, 4H), 4.00 (p, *J*=6.9 Hz, 1H), 3.54 (dd, *J*=16.9, 7.0 Hz, 2H), 3.38 (dd, *J*=16.9, 6.8 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 150.4, 141.2, 139.7, 136.9, 129.6, 129.2, 127.2, 123.9, 45.3, 36.6, 21.0; HRMS calcd for $C_{24}H_{21}N_2O_6^+$ $[M+H]^+$ 433.1397, found: 433.1394.

*4.2.18. 1,5-Di(thiophen-2-yl)-3-(p-tolyl)pentane-1,5-dione (**3r**).* Creamy white solid; yield 66%, mp: 92.8–93.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.66 (m, 2H), 7.67–7.55 (m, 2H), 7.22–7.13 (m, 2H), 7.13–7.05 (m, 4H), 4.01 (p, *J*=7.1 Hz, 1H), 3.41 (dd, *J*=16.0, 7.0 Hz, 2H), 3.25 (dd, *J*=16.0, 7.2 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 144.3, 140.2, 136.4, 133.7, 132.2, 129.4, 128.2, 127.3, 45.5, 37.6, 21.0; HRMS calcd for $C_{20}H_{19}O_2S_2^+$ $[M+H]^+$ 355.0825, found: 355.0821.

*4.2.19. 3-(4-Chlorophenyl)-1,5-bis(4-methoxyphenyl)pentane-1,5-dione (**3s**).* Green solid; yield 52%, mp: 62.1–62.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–7.75 (m, 4H), 7.22 (s, 4H), 7.05–6.75 (m, 4H), 4.02 (p, *J*=7.1 Hz, 1H), 3.85 (s, 6H), 3.42 (dd, *J*=16.4, 6.8 Hz, 2H), 3.24 (dd, *J*=16.4, 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9,

163.6, 142.5, 132.2, 130.4, 129.9, 128.9, 128.7, 113.8, 55.5, 44.5, 37.0; HRMS calcd for $C_{25}H_{24}ClO_4^+$ $[M+H]^+$ 423.1360, found: 423.1358.

*4.2.20. 1,5-Bis(4-bromophenyl)-3-(4-chlorophenyl)pentane-1,5-dione (**3t**).* White solid; yield 77%, mp: 98.8–100.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 4H), 7.64–7.55 (m, 4H), 7.29–7.15 (m, 4H), 4.00 (p, J=6.9 Hz, 1H), 3.44 (dd, J=16.8, 6.8 Hz, 2H), 3.26 (dd, J=16.8, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 141.9, 135.4, 132.6, 132.0, 129.6, 128.9128.8, 128.5, 44.6, 36.5; HRMS calcd. For $C_{23}H_{18}Br_2ClO_2^+$ $[M+H]^+$ 518.9346, found: 518.9357.

*4.2.21. 3-(4-Chlorophenyl)-1,5-di-p-tolylpentane-1,5-dione (**3u**).* White solid; yield 94%, mp: 86.8–87.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J=8.2 Hz, 4H), 7.30–7.16 (m, 8H), 4.03 (p, J=7.0 Hz, 1H), 3.44 (dd, J=16.6, 6.8 Hz, 2H), 3.28 (dd, J=16.6, 7.3 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 144.1, 142.5, 134.3, 132.3, 129.3, 128.9, 128.7, 128.3, 44.7, 36.7, 21.7; HRMS calcd for $C_{25}H_{24}ClO_2^+$ $[M+H]^+$ 391.1461, found: 391.1459.

4.3. Capture of key intermediate 7

A 10 mL tube was charged with *p*-tolualdehyde (0.5 mmol), acethydrazide (0.5 mmol), CH_3OH 5 mL and a stir bar. The reaction was heated to 50 °C for 4 h (**1** was formed). Then 1,2-diamine catalyst (0.5 mmol), 2,6-difluorobenzoic acids (1 mmol), TEA (0.5 mmol) and acetophenone (**2**, 2 mmol) were added to the reaction and the mixture was stirred at 50 °C for 72 h. The resulting mixture was allowed to cool down to room temperature. The mixture was then purified by column chromatography on silica gel (PE–EtOAc=4:1) to get the intermediate **7c**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66–7.51 (m, 4H), 7.29 (t, J=7.6 Hz, 4H), 7.23 (td, J=7.2, 1.2 Hz, 2H), 7.04 (dd, J=24.0, 8.0 Hz, 4H), 4.89 (t, 1H), 3.50 (dt, J=9.2, 6.6 Hz, 1H), 3.15–2.92 (m, 2H), 2.94–2.82 (m, 2H), 2.35 (ddd, J=12.3, 5.6, 1.1 Hz, 1H), 2.23 (s, 3H), 2.13 (m, J=8.2, 7.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 144.8, 142.3, 139.6, 135.7, 129.1, 128.3, 128.2, 127.8, 127.4, 127.3, 127.1, 125.9, 107.8, 80.6, 52.2, 44.2, 41.5, 38.7, 21.0. ESI calcd. For $C_{26}H_{26}N_2^+$ $[M+H]^+$ 366.61, found: 366.67.

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Supplementary data

The original data of ^{1}H NMR and ^{13}C NMR of all products are supplied. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.10.009. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. For reviews, and recent examples, see: (a) Trost, B. M.; Heathcock, C. H.; Fleming, I.; *Comprehensive Organic Synthesis*, 1st ed., 1991, Vol. 2, p 133; (b) Trost, B. M.; Semmelhack, M. F.; Fleming, I.; *Comprehensive Organic Synthesis*, 1st ed., 1991, Vol. 4, p 1; (c) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582–2590; (d) Zhang, F.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097–1100; (e) Li, N.; Zhang, X.; Xu, X.; Chen, Y.; Qiu, R.; Chen, J.; Wang, X.; Yin, S. *Adv. Synth. Catal.* **2013**, *355*, 2430–2440; (f) Fan, W.; Li, W.; Ma, X.; Tao, X.; Li, X.; Yao, Y.; Xie, X.; Zhang, Z. *Chem. Commun.* **2012**, 4247–4249.
2. (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179–180; (b) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979–2990; (c) Cheng, X.; Hoger, S.; Fenske, D. *Org. Lett.* **2003**, *5*, 2587–2589; (d) Smith, N. M.; Raston, C. L.; Smith, B. C.; Sobolev, A. N. *Green Chem.* **2007**, *9*, 1185–1190; (e) Takita, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 2068–2070; (f) Liu, R.; Zhang, J. *Org. Lett.* **2013**, *15*, 2266–2269.
3. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1992; (b) Leonard, J. *Contemp. Org. Synth.* **1994**, 387–415; (c) Leonard, J.; D'ıez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, *10*, 2051–2061; (d) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part B: Reaction and Synthesis*, 4th ed.; Springer, 2002; (e) Ono, N.; Miyake, H.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1983**, 875–876; (f) Kumar, T. P.; Sattar, M. A.; Sarma, V. U. M. *Tetrahedron: Asymmetry* **2013**, *24*, 1615–1619; (g) Kumaraswamy, G.; Jena, N.; Sastry, M. N. V.; Padmaja, M.; Markondaiah, B. *Adv. Synth. Catal.* **2005**, *347*, 867–871; (h) Wang, X.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem.* **2003**, *68*, 10046–10057; (i) Harada, T.; Adachi, S.; Wang, X. *Org. Lett.* **2004**, *6*, 4877–4879; (j) Wang, W.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 1637–1639; (k) Liu, D.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 8160–8161; (l) Takenaka, N.; Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 742–743.
4. (a) Shimizu, S.; Shirakawa, S.; Suzuki, T.; Sasaki, Y. *Tetrahedron* **2001**, *57*, 6169–6173; (b) Silva, A. M. S.; Almeida, L. M. P. M.; Tavares, H. R.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **1999**, 1739–1744; (c) Yanagisawa, A.; Takahashi, H.; Arai, T. *Tetrahedron* **2007**, *63*, 8581–8585; (d) Waldmann, H.; Karunakar, G. V.; Kumar, K. *Org. Lett.* **2008**, *10*, 2159–2162.
5. (a) Yang, J.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453–455; (b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470; (c) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; (d) Jiang, J.; Cai, Y.; Chen, W.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* **2011**, 4016–4018; (e) Mahe, O.; Dez, I.; Levacher, V.; Briere, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7072–7075; (f) Tsakos, M.; Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2012**, *354*, 740–746.
6. For our previous work see: (a) Wang, J.; Wang, X.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, 1751–1753; (b) Wang, J.; Li, Q.; Qi, C.; Liu, Y.; Ge, Z.; Li, R. *Org. Biomol. Chem.* **2010**, *8*, 4240–4242; (c) Wang, J.; Qi, C.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, 2124–2126; (d) Wang, W.; Wang, J.; Zhou, S.; Sun, Q.; Ge, Z.; Wang, X.; Li, R. *Chem. Commun.* **2013**, 1333–1335.
7. Wang, J.; Lei, M.; Li, Q.; Ge, Z.; Wang, X.; Li, R. *Tetrahedron* **2009**, *65*, 4826–4833.
8. Li, X.; Wang, C.; Jin, J.; Xue, X.; Cheng, J. *Chem.—Asian. J.* **2013**, *8*, 997–1003.