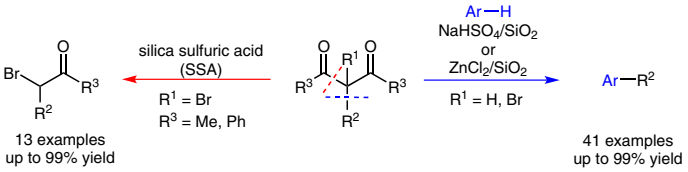
Synthesis T. Aoyama et al. Special Topic

Simple Method for sp^2–sp^3 and sp^3–sp^3 Carbon–Carbon Bond Activation in 2-Substituted 1,3-Diketones

Tadashi Aoyama[*a,b]
Mamiko Hayakawa[a]
Sho Kubota[a]
Sumire Ogawa[a]
Erika Nakajima[a]
Emi Mitsuyama[a]
Taku Iwabuchi[a]
Haruki Kaneko[a]
Rina Obara[a]
Toshio Takido[a]
Mitsuo Kodomari[c]
Akihiko Ouchi[a]

[a] Department of Materials and Applied Chemistry, College of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan
aoyama.tadashi@nihon-u.ac.jp
[b] The Center for Creative Materials Research, Research Institute of Science and Technology, College of Science and Technology, Nihon University, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan
[c] The Institute of Natural Sciences, College of Humanities and Science, Nihon University, Sakurajosui, Setagaya-ku, Tokyo 156-8550, Japan



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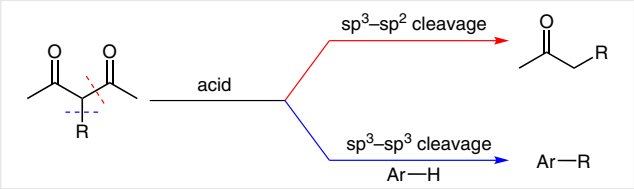
Abstract Simple and efficient methods were developed for sp^2–sp^3 and sp^3–sp^3 C–C bond-activation reactions of 2-substituted 1,3-diketones. 3-Substituted 3-bromopentane-2,4-diones were deacylated in the presence of an aromatic compound and a silica gel supported Brønsted acid containing sulfonic groups. The carbocation formed by cleavage of the sp^3–sp^3 C–C bond of the dione alkylated the aromatic compound.

Key words bond activation, alkylations, deacylations, heterogeneous reactions

Selective C–C and C–H bond activation has attracted increasing attention in relation to organic synthesis.[1] Compared with C–H bond activation, selective activation of C–C bonds is more difficult to achieve owing to their relatively high strength and their its weak interactions with metal catalysts. Consequently, many researchers have examined C–C bond activation and its applications. Commonly used methods for activation of C–C bonds include the use of ring-strained molecules,[2] direction by chelation assistance,[3] and the use of molecules containing sp^2–sp^3 or sp–sp^3 C–C bonds,[4] among others.[5] As an example of the use of molecules containing sp^2–sp^3, 1,3-diketones, which are readily available, have been used as starting materials in organic synthesis.[6] In the first half of 20th century, both acidic and basic activations of sp^2–sp^3 C–C bonds in 1,3-dicarbonyl compounds was studied by Adkins and co-workers.[7] However, bases are generally used in deacylations through sp^2–sp^3 C–C bond activation.[8] Recently, 1,3-dicarbonyl compounds have been used as acylating agents. For example, Takai and co-workers reported an indium(III) triflate-catalyzed acylation of alcohols or amines through sp^2–sp^3 C–C bond cleavage of 1,3-diketones;[9] a modified method using iron(III) chloride has been reported by Jana and co-workers.[10] Additionally, a copper-catalyzed arylation of 1,3-diketones with aryl halides to give α-aryl ketones was reported by Lei and co-workers in 2010.[11] Later, a method for the synthesis of isocoumarins through copper iodide-catalyzed tandem acylation and cyclization was developed by Fan,[12] Xi,[13] and Yao,[14] and their respective co-workers. Wang and co-workers recently reported syntheses of amides, α-keto amides, and 1*H*-pyrrol-3(2*H*)-ones from amines and 1,3-diketones, in which the cleavage of C–C bonds was mediated by peroxides.[15] We have previously reported a deacylation of 1,3-dicarbonyl compounds by using a solid-supported inorganic base (sodium carbonate/alumina).[16] We also reported that the sp^3–sp^2 C–C bond of α-bromo β-diketones was activated by the presence of silica sulfuric acid (SSA).[17] During this study, we unexpectedly found that the sp^3–sp^3 C–C bond of 3-(diphenylmethyl)pentane-2,4-dione was cleaved in the presence of a Brønsted acid in benzene to form a diphenylmethyl cation that reacted with benzene to give triphenylmethane (Scheme 1).[18]

Li et al.[19] reported that the C–C bond in a compound containing a dibenzoylmethyl unit as a leaving group was activated by iron(III) chloride, whereas the C–C bond in a compound containing a diacetylmethyl group was not activated. Here, we report both sp^2–sp^3 and sp^3–sp^3 C–C bond

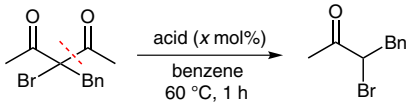


Scheme 1

activations of 3-substituted pentane-2,4-diones by using inorganic solid-supported Lewis or Brønsted acids.

First, we examined sp^2–sp^3 C–C bond activation in 3-benzyl-3-bromopentane-2,4-dione (**1a**) in the presence of various acids (Table 1). SSA showed the highest activity among the solid acids tested (Table 1, entry 1). SSA was easily recovered, but the recovered SSA could not be reused for subsequent reactions. Other solid acids were ineffective (entries 2–6). However, sodium bisulfate/silica gel and Amberlyst 15 were mildly effective in C–C bond activation of dione **1a**, and gave the deacylated product **2a** in low yields of 17% and 2%, respectively. In reactions using a homogeneous catalyst, sulfuric acid showed a similar catalytic activity to SSA but gave a lower yield of **2a** as a result of undesirable side reactions. When hydrochloric acid or 4-toluenesulfonic acid was used as the acid catalyst, **1a** was recovered quantitatively.

Table 1 sp^2–sp^3 C–C Bond Activation of Dione **1a** with Various Acids



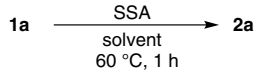
1a **2a**

Entry	Acid	*x* mol%	Yield[a] (%)	
			1a	**2a**
1	SSA	185	–	100
2	$NaHSO_4/SiO_2$	210	83	17
3	Amberlyst 15	480	98	2
4	$HClO_4/SiO_2$	10	100	–
5	PPA/SiO_2	–[b]	100	–
6	$ZnCl_2/SiO_2$	150	100	–
7	H_2SO_4	900	–	85
8	HCl	600	100	–
9	PTSA	100	100	–

[a] The recovery and yield were determined from the GLC area ratio.
[b] 0.3 g of PPA was used.

Next, we tested several solvents for this reaction (Table 2). 1,2-Dichloroethane was the most suitable, solvent (Table 2, entry 4) whereas toluene showed no formation of **2a** (entry 2). The absence of **2a** in toluene was explained by the sulfonation of the aromatics with SSA; when a suspension of SSA in toluene was stirred at 80 °C for five hours 4-toluenesulfonic acid was obtained in good yield, a result that agreed with that reported by Hajipour et al.[20] Therefore, in the reaction of dione **1a** in the presence of SSA in toluene, the SSA was predominately consumed in the sulfonation of toluene rather than in the activation of the C–C bond of dione **1a**. The resulting 4-toluenesulfonic acid was ineffective in C–C bond activation of dione **1a**.

Table 2 sp^2–sp^3 C–C Bond Activation of Dione **1a** in Various Solvents

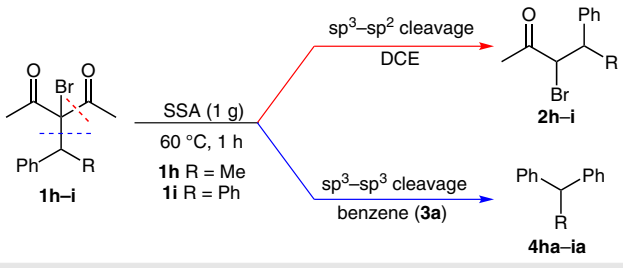


Entry	Solvent	Conv. (%)	Yield[a] (%)
1	benzene	100	79
2	toluene	4	–[b]
3	PhCl	100	85
4	DCE	100	92
5	hexane	100	69

[a] Isolated yield.
[b] Not determined.

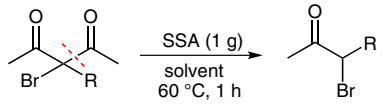
Next, we explored the deacylation of various 3-substituted 3-bromopentane-2,4-diones **1** with SSA in benzene or 1,2-dichloroethane (Table 3). The length of alkyl groups at the 3-position in dione **1** did not affect the deacylation in either solvent (entries 1–4). The reaction of dione **1e**, which has a bromine atom in the ω-position, gave the corresponding deacylated product **2e** in 92 and 94% yield in benzene and 1,2-dichloroethane, respectively (entry 5). The expected product **2f** from the reaction of the ester-containing dione **1f** was not obtained in either solvent (entry 6).

When the reactions of 2,4-pentanediones **1h** and **1i**, which have a *sec*-alkyl group at the 3-position, were carried out in 1,2-dichloroethane at 60 °C for one hour, the deacylated products **2h** and **2i** were obtained in low to moderate yields. Although **2h** and **2i** were not obtained in benzene, 1,1-diphenylethane (**4ha**) and triphenylmethane (**4ia**) were formed quantitatively from **1h** and **1i**, respectively, through cleavage of the sp^3–sp^3 C–C bond (entries 8, 9 and Scheme 2); the cleavage of the sp^3–sp^3 C–C bond is discussed below.



Scheme 2

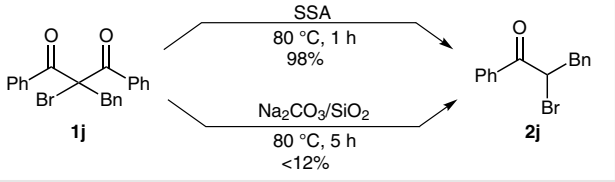
Table 3 Deacetylation of **1** with SSA



Entry	R	Product	Yield[a] (%)	
			Benzene	DCE
1	Bn	**2a**	79	92
2	$Ph(CH_2)_2$	**2b**	77	77
3	$Me(CH_2)_7$	**2c**	95	99
4	$Me(CH_2)_{17}$	**2d**	92	99
5	$Br(CH_2)_5$	**2e**	92	94
6	$EtO_2C(CH_2)_3$	**2f**	–	–
7	Ph	**2g**	80	99
8	PhCH(Me)	**2h**	–	11[b]
9	Ph_2CH	**2i**	–	49

[a] Isolated yield.
[b] Yield was determined by GLC.

Deacylations of 1,3-dicarbonyl compounds have generally been carried out under basic conditions.[9] In contrast, we found that SSA was more effective than bases for the deacylation of dibenzoyl methyl derivatives. For instance, the reaction of 2,2-dibenzyl-1,3-diphenylpropane-1,3-dione (**1j**) in the presence of SSA gave 2-bromo-1,3-diphenylpropan-1-one (**2j**) in quantitative yield after one hour at 80 °C, whereas sodium carbonate/silica gel gave ketone **2j** in 12% yield after five hours at 80 °C (Scheme 3).

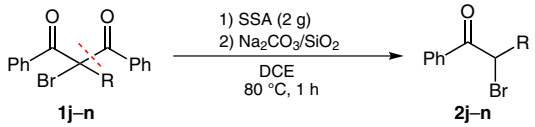


Scheme 3 Effectiveness of SSA for the conversion of dione **1j** into ketone **2j**

When the reactions of the 2-bromo-1,3-diphenyl-1,3-diones **1j**–**n** were carried out in the presence of SSA in 1,2-dichloroethane at 80 °C for one hour (Table 4), the diones were debenzoylated to give corresponding products **2j**–**n**, together with small amounts of benzoic acid. The latter was easily removed from the reaction mixture by the addition of sodium carbonate/silica gel.

The bromine atom in dicarbonyl compounds played an important role in the sp^2–sp^3 bond activation. When a mixture of SSA and 3-benzylpentane-2,4-dione in benzene was stirred at 80 °C for one hour, no deacylated products were observed. On the basis of this result, we developed a tandem bromination–deacylation reaction to give bromo ketones **2** from the corresponding 3-substituted pentane-2,4-diones in one pot (Table 5). All the substrates employed underwent bromination and deacylation to give the expected α-bromo ketones **2** in moderate to good yields.

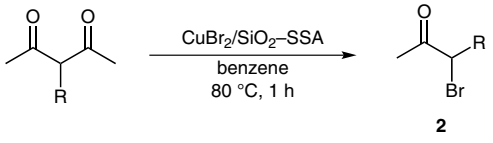
Table 4 Debenzoylation of Diones **1** with SSA



Entry	R	Product	Yield[a] (%)
1	Bn	**2j**	98
2	Me	**2k**	79
3	$4\text{-}MeC_6H_4CH_2$	**2l**	44
4	$4\text{-}ClC_6H_4CH_2$	**2m**	92
5	$Me(CH_2)_7$	**2n**	99

[a] Isolated yield.

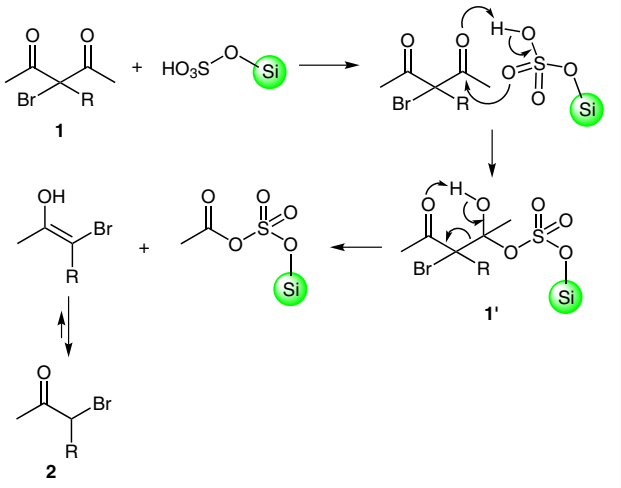
Table 5 Preparation of Bromo Ketones **2** by a Tandem Reaction



Entry	R	Product	Yield[a] (%)
1	Bn	**2a**	74
2	$Ph(CH_2)_2$	**2b**	71
3	$Me(CH_2)_7$	**2c**	96
4	$Br(CH_2)_5$	**2e**	91
5	Ph	**2g**	62

[a] Isolated yield

Acid-catalyzed deacylation of 1,3-dicarbonyl compounds is generally promoted by alcohols, but our procedure does not require an alcohol. We propose a tentative pathway (Scheme 4) for the formation of bromo ketone **2** by sp^2–sp^3 C–C bond activation and cleavage, on the basis of the following results: (a) SSA cannot be reused for subsequent reactions, (b) the reaction proceeds only when an acid containing a sulfonic group is used as the catalyst, and (c) the presence of a bromine atom at the 3-position is required. In our proposed mechanism, the sulfonyl ester **1′** is formed via a six-membered-ring transition state. The sulfonyl oxygen attacks the carbonyl carbon, which is activated both by protonation of the oxygen atom and by the inductive effect of the bromine atom. Subsequently, the C–C bond in ester **1′** is cleaved to form an enol that isomerizes to give the bromo ketone **2**.

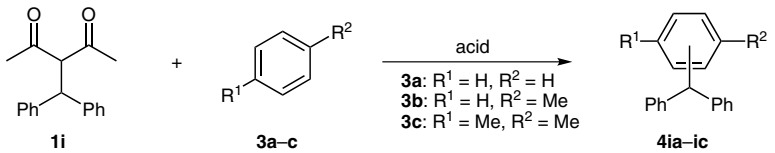


Scheme 4 Tentative pathway for sp^2–sp^3 C–C bond activation

In the reaction of α-bromo-1,3-diketones with SSA in aromatic solvents, the sp^3–sp^3 C–C bond was cleaved in preference to the sp^2–sp^3 C–C bond, resulting in the formation of the corresponding triarylmethane (Scheme 2). A similar activation of a C–C bond in 2-substituted 1,3-diphenyl-1,3-diones by using iron(III) chloride has been reported by Li et al.,[19] who mainly used a dibenzoylmethyl unit as the leaving group to give a stoichiometric amount of dibenzoylmethane and the expected products. We therefore focused our attention on developing a simple procedure for activation of sp^3–sp^3 C–C bonds.

In the case of sp^3–sp^3 C–C bond activation in 2-substituted 1,3-dicarbonyl compounds, the presence of a bromine atom was not important. For example, when a mixture of 3-(diphenylmethyl)pentane-2,4-dione (**1i**) and SSA in benzene was stirred at 60 °C for one hour, triphenylmethane (**4ia**) was obtained in 74% yield along with pentane-2,4-dione (Table 6, entry 1). When similar reactions were performed in the presence of sodium bisulfate/silica gel or zinc chloride/silica gel instead of SSA, only traces of **4ia** were obtained (entries 2 and 3). The sp^3–sp^3 C–C bond activation was facilitated by increasing the electron density in the aromatic reactant. When the reactions were carried out in toluene using various acids, 1-(diphenylmethyl)-4-methylbenzene (**4ib**) was obtained in all cases. Although, SSA was the most effective of the acids used, we avoided its use in subsequent reactions because sulfonation of **3b** occurred besides activation of the sp^3–sp^3 C–C bonds (entry 4). Acids such as sulfuric acid, sodium bisulfate/silica gel, Amberlyst15, poly(phosphoric acid)/silica gel, or zinc(II) chloride/silica gel promoted this reaction and gave triaryl **4ib** in good to excellent yield (entries 5–9). In the reactions of xylene, a large excess of *p*-xylene in relation to **1i** was needed to obtain triaryl **4ic** in excellent yield (entry 10), whereas

Table 6 Reactions of 3-(Diphenylmethyl)pentane-2,4-dione (**1i**) with Aromatic Hydrocarbons in the Presence of Various Acids



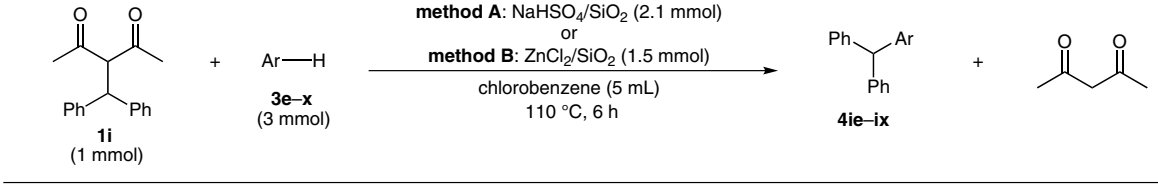
1i (1 mmol) + **3a–c** (5 mL) → **4ia–ic**

Entry	R^1	R^2	Acid	Temp (°C)	Time (h)	Yield[a] (%)
1	H	H	SSA	60	1	74
2	H	H	$NaHSO_4/SiO_2$	60	5	trace
3	H	H	$ZnCl_2/SiO_2$	60	5	trace
4	Me	H	SSA	60	1	99
5	Me	H	H_2SO_4	110	5	66
6	Me	H	$NaHSO_4/SiO_2$	110	5	90
7	Me	H	Amberlyst 15	110	5	85
8	Me	H	PPA/SiO_2	110	5	40
9	Me	H	$ZnCl_2/SiO_2$	110	5	90
10	Me	Me	$NaHSO_4/SiO_2$	110	5	92

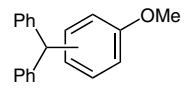
[a] Isolated yield.

the reaction of **1i** with three equivalents equiv of mesitylene (**3d**) gave 2-(diphenylmethyl)-1,3,5-trimethylbenzene (**4id**) in 61% yield after six hours.

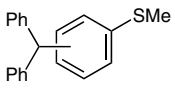
Next, we examined the alkylation of various aromatics with 2-substituted 1,3-diketone in the presence of sodium bisulfate/silica gel or zinc(II) chloride/silica gel (Scheme 5). The general procedure was as follows. A mixture of dione **1i** (1 mmol), aromatic hydrocarbon **3** (3 mmol), and sodium bisulfate/silica gel (1 g, 2.1 mmol) in chlorobenzene (5 mL) was stirred at 110 °C for six hours. The results are shown in Scheme 5. Anisole (**3e**) and thioanisole (**3f**) gave the corresponding triarylmethanes **4ie** and **4if**, respectively, in excellent yields. Alkylation of **3e** and **3f** occurred selectively at the 4-position on their rings. Sodium bisulfate/silica gel and zinc(II) chloride/silica gel both promoted the reaction of dione **1i** with phenol (**3g**) to give **4ig** in excellent yields. The selectively of alkylation at the 4-position increased when zinc(II) chloride/silica gel was used instead of sodium bisulfate/silica gel. The reaction of benzenethiol (**3h**) in the presence of sodium bisulfate/silica gel did not give the expected product **4ih** but, instead, diphenylmethyl phenyl sulfide was obtained in excellent yield. This result can be explained by attack of the carbocation resulting from the cleavage of sp^3–sp^3 C–C bond in **1i** on the sulfur atom in **3h**, which has a higher nucleophilicity than the aromatic carbons (Scheme 6).



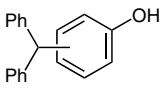
(method): yield (%)



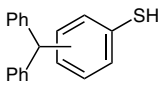
4ie
(A): 90% (2-/4- = 1:9.5)



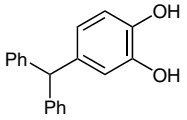
4if
(A): 91% (2-/4- = 1:18)



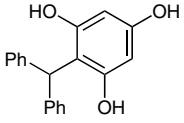
4ig
(A): 85% (2-/4- = 1:2.4)
(B): 95% (2-/4- = 1:7.6)



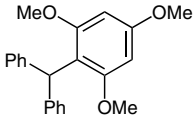
4ih
(A): ND (84%)



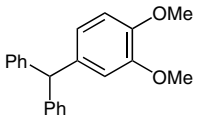
4ii
(A): 89%



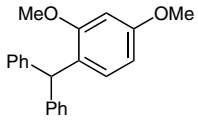
4ij
(A): no reaction



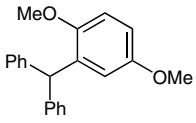
4ik
(A): 86%



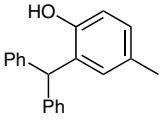
4il
(A): 99%



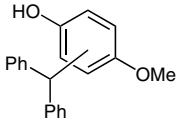
4im
(A): 86%



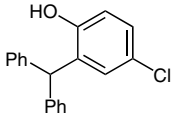
4in
(A): 82%



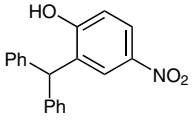
4io
(A): 91%
(B): 94%



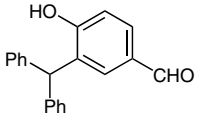
4ip
(A): 90% (2-/3- = 12:1)
(B): 92% (2-/3- = 2.7:1)



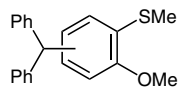
4iq
(A): 84%



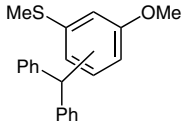
4ir
(A) (130 ° C, 24 h): 30% (30%)*
(B) (130 °C, 72 h): 51% (17%)*
* yield of deacylated product **2**



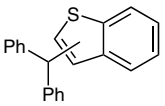
4is
(A) (130 °C, 24 h): trace
(B) (130 °C, 24 h): 26%



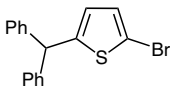
4it
(A) (5 h): 99% (4-/5- = 2.5:1)



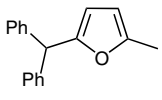
4iu
(A) (5 h): 94%



4iv
(A) (3 h): 98% (2-/3- = 8:1)
(B) (2 h): 99% (2-/3- = 4.3:1)

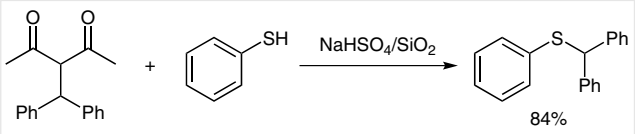


4iw
(A): 82%
(B): 92%

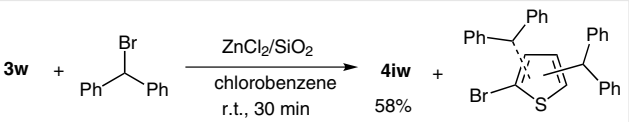


4ix
(A): 4%
(B): 97%

Scheme 5



Scheme 6

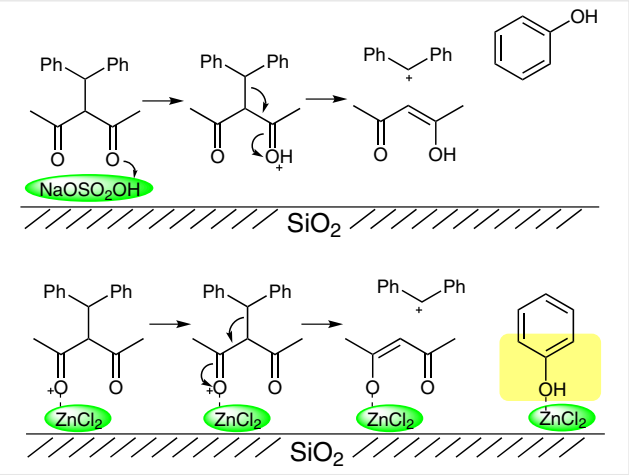


Scheme 7

When the reactions of catechol (**3i**) and benzene-1,3,5-triol (**3j**) with dione **1i** were carried out under the same conditions, **3i** gave the corresponding diol **4ii** in 89% yield. In contrast **4ij** was not obtained from the reaction of **3j**. 1,3,5-Trimethoxybenzene (**3k**) and dimethoxybenzenes **3l**, **3m**, and **3n** reacted readily with dione **1i** to give the corresponding triarylmethanes **4ik** and **4il**–**in** in good yields. The reactions of several 4-substituted phenols **3o**–**s** were also examined. The reactions of 4-methylphenol (**3o**) in the presence of sodium bisulfate/silica gel or zinc(II) chloride/silica gel gave **4io** in 91% and 94%, respectively, whereas the reaction of 4-methoxyphenol (**3p**) gave mixtures of 2- and 3-(diphenylmethyl)-4-methoxyphenol **4ip** in total yields of 90% and 92%, respectively; the ratio of the 2-isomer to the 3-isomer was 12:1 with sodium bisulfate/silica gel and 2.7:1 with zinc(II) chloride/silica gel. 4-Nitrophenol (**3r**) required a higher reaction temperature and a longer reaction time for complete consumption of the reactant. When the reaction was carried out in the presence of sodium bisulfate/silica gel at 130 °C for 24 hours, the desired product **4ir** was obtained in 30% yield, along with deacylated product **2i**. The corresponding reaction with zinc(II) chloride/silica gel required a longer time and gave **4ir** in 51% yield. The reaction of 4-hydroxybenzaldehyde (**3s**) was not promoted by sodium bisulfate/silica gel but the reaction on zinc(II) chloride/silica gel at 130 °C for 24 hours gave **4is** in 26%. 2-(Methylsulfanyl)anisole (**3t**) and 3-(methylsulfanyl)anisole (**3u**) were alkylated to give ether sulfides **4it** and **4iu**, respectively, both as mixtures of the 4- and 5-alkylated compounds. The reaction of 1-benzothiophene (**3v**) proceeded in the presence of sodium bisulfate/silica gel or zinc(II) chloride/silica gel to give product **3iv** quantitatively after three and two hours, respectively. The regioselectivity of the reaction using sodium bisulfate/silica gel was higher than that of the reaction using zinc(II) chloride/silica gel, in which alkylation at the 2-position predominated over that at the 3-position. In the reactions of five-membered heterocycles, 2-bromothiophene (**3w**) gave **4iw** in good to excellent yield on sodium bisulfate/silica gel or zinc(II) chloride/silica gel, whereas 2-methylfuran (**3x**) gave a poor yield of **4ix** with sodium bisulfate/silica gel but gave a quantitative yield on zinc(II) chloride/silica gel.

To demonstrate that this alkylation is complementary to the classical Friedel–Crafts alkylation, we carried out the reaction of **3w** with bromo(diphenyl)methane using zinc(II) chloride/silica gel as a Lewis acid. The product **4iw** was obtained in 58% yield, along with its regioisomer and various polyalkylated products (Scheme 7).

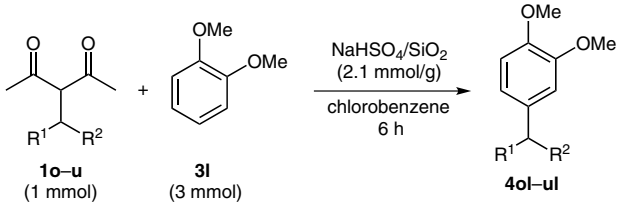
The differences of selectivity in the reaction of **3g**, **3p**, or **3v** with dione **1i** in the presence of sodium bisulfate/silica gel compared with those in the presence of zinc(II) chloride/silica gel might be the result of interactions between the heteroatoms and the surface of the solid-supported acids. The reactions probably proceeded as follows. In the reaction using sodium bisulfate/silica gel, the dicarbonyl compound **1i** approaches the solid surface and the sp^3–sp^3 C–C bond is cleaved to form a carbocation that reacts with the aromatic (**3g**, **3p**, or **3v**), whereas in the case of zinc(II) chloride/silica gel, the carbonyl oxygen chelates with the zinc atom to generate a carbocation and the hetero atom in the aromatic is simultaneously adsorbed on the solid surface. This chelation between the hetero atom in the aromatic and the zinc atom results in suppression of alkylation at the carbon close to the heteroatom as a result of steric hindrance (Scheme 8).



Scheme 8

We then extended the method to the alkylation of 1,2-dimethoxybenzene (**3l**) with several 3-substituted pentane-2,4-diones **1o**–**u** (Table 7). The reaction of 3-(1-phenylethyl)pentane-2,4-dione (**1o**) with **3l** at 110 °C for six hours gave diether **4ol** in 45% yield (Table 7, entry 1). The yield of diether **4ol** increased to 80% when the reaction was carried out at 130 °C in the presence of 2 g of sodium bisulfate/silica gel (entry 2). The reaction of **3l** with dione **1p** under the same conditions gave the corresponding alkylated product in 41% yield, together with 1,1-[bis(3,4-dimethoxyphenyl)]ethane (**5**) (entry 4).

Table 7 Alkylation of 1,2-Dimethoxybenzene (**3l**) with Various Diketones



1o–u (1 mmol) + **3l** (3 mmol) → **4ol–ul**

Entry	R^1	R^2	Temp (°C)	Acid (g)	Product	Yield (%)
1	Ph	Me	110	1.0	**4ol**	45
2	Ph	Me	130	2.0	**4ol**	80
3	4-$MeOC_6H_4$	Me	110	1.0	**4pl**	71
4	4-$MeOC_6H_4$	Me	130	2.0	**4pl**	41
5	4-ClC_6H_4	Me	130	3.5	**4ql**	75
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	110	1.0	**4rl**	80
7	4-ClC_6H_4	4-ClC_6H_4	130	2.0	**4sl**	96
8	Ph	4-$MeOC_6H_4$	110	1.0	**4tl**	94
9	Ph	4-ClC_6H_4	130	1.0	**4ul**	97

When a mixture of dione **4pl**, catechol (**3lb**), and sodium bisulfate/silica gel in chlorobenzene was stirred at 130 °C for six hours, tetraether **5** was observed in the reaction mixture (Scheme 9). To avoid further conversion of **4pl** into **5**, the reaction was carried out under milder condition to give **4pl** in 71% yield (entry 3). The presence of electron-donating substituents on the aromatic ring increased the reactivity of **1**. For example, **1r**, containing methoxy substituent on the ring, reacted with dione **3l** at 110 °C to give **4rl** in 80% yield, whereas **1s** containing a chlorine atom on the ring required a large excess of sodium bisulfate/silica gel and a higher reaction to give diether **4sl** in excellent yield (entries 6 and 7).

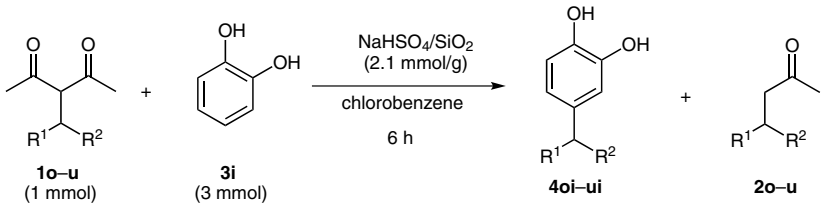
Scheme 9

In contrast to the efficient alkylation of 1,2-dimethoxybenzene (**3l**) with diketones **1o–u** (Table 7), alkylation of catechol (**3i**) did not give the corresponding triarylmethane in satisfactory yields under similar conditions (Table 8). In some reactions, deacylation occurred by a sp^2–sp^3 C–C bond activation to give the corresponding ketone **2** as the main product, together with 2-hydroxyphenyl acetate (entries 1 and 3).

On the basis of these results, we propose a plausible reaction pathway (Scheme 10). Activation of the sp^2–sp^3 C–C bond is triggered by a nucleophilic attack by a hydroxy oxygen in **3i** on the carbonyl carbon activated by the acid. Similar reactions using iron(III) chloride or iron(III) triflate have recently been reported.[10] In the case of activation of the sp^3–sp^3 C–C bond, the carbonyl oxygen of diketone **1** is protonated, and subsequently an enol and a diphenylmethyl cation are formed. The resulting carbocation reacts with aromatic **3** to afford the triarylmethane **4**. The ratio of cleavage of sp^2–sp^3 to sp^3–sp^3 C–C bonds might be dependent on the stability of the resulting carbocation. The reactions of **1** containing benzhydryl groups gave the expected triarylmethanes **4** as the main products.

To compare the applicability of Brønsted and Lewis acids, we examined the reactions of 4-(2-haloethyl)phenols **6a** and **6b** with dione **1i** in the presence of sodium bisulfate/silica gel or zinc(II) chloride/silica gel (Scheme 11). In the reaction of 4-(2-chloroethyl)phenol (**6a**) with dione **1i** in the presence of sodium bisulfate/silica gel, the 2-alkylated product **7ia** was formed quantitatively, whereas a lower yield of **7ia** was obtained with zinc(II) chloride/silica gel. The reaction of 2-(2-bromoethyl)phenol (**6b**) with **1i** in the presence of sodium bisulfate/silica gel gave product **7ib** in 75% yield as the sole alkylation product, whereas a mixture of **7ib** and **7ia** was obtained with zinc(II) chloride/silica gel, probably by a halogen-exchange reaction.

Table 8 Alkylation of Catechol with Various Diketones



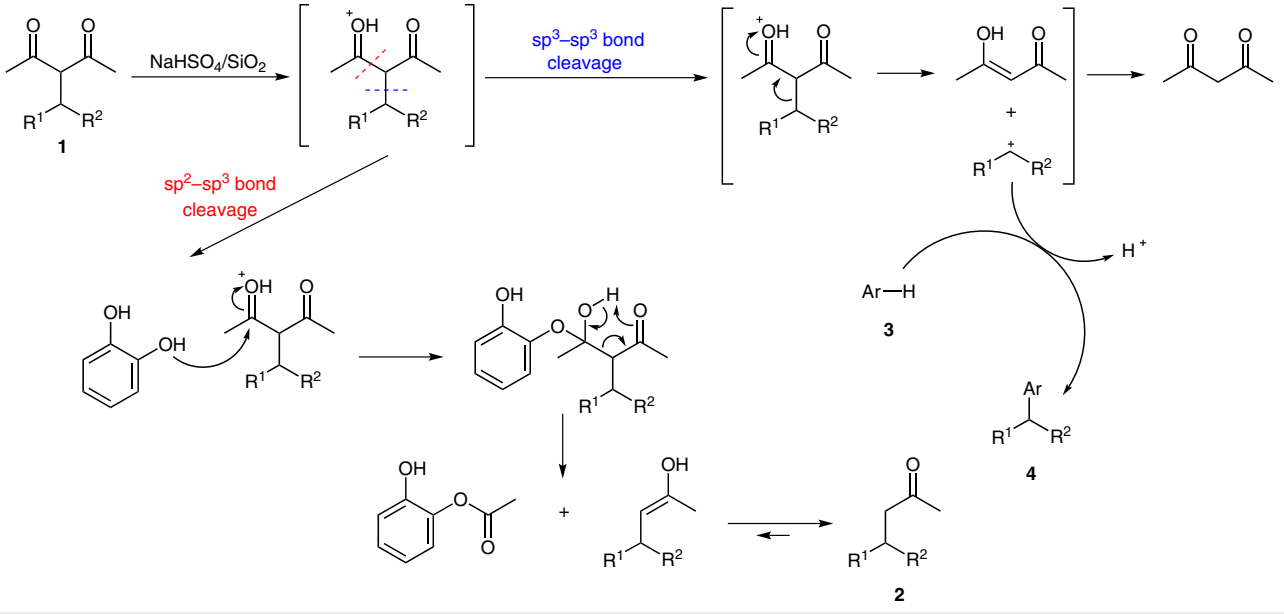
1o–u (1 mmol) + **3i** (3 mmol) → **4oi–ui** + **2o–u**

Entry	R^1	R^2	Temp (°C)	Acid (g)	Product	Yield (%)	Product	Yield (%)
1	Ph	Me	130	2.0	**4oi**	20	**2o**	66
2	4-$MeOC_6H_4$	Me	110	1.0	**4pi**	37	**2p**	–
3	4-ClC_6H_4	Me	130	2.0	**4qi**	10	**2q**	51
4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	110	1.0	**4ri**	67	**2r**	–
5	4-ClC_6H_4	4-ClC_6H_4	130	2.0	**4si**	57	**2s**	17
6	Ph	4-$MeOC_6H_4$	110	1.0	**4ti**	66	**2t**	–
7	Ph	4-ClC_6H_4	130	1.0	**4ui**	70	**2u**	8

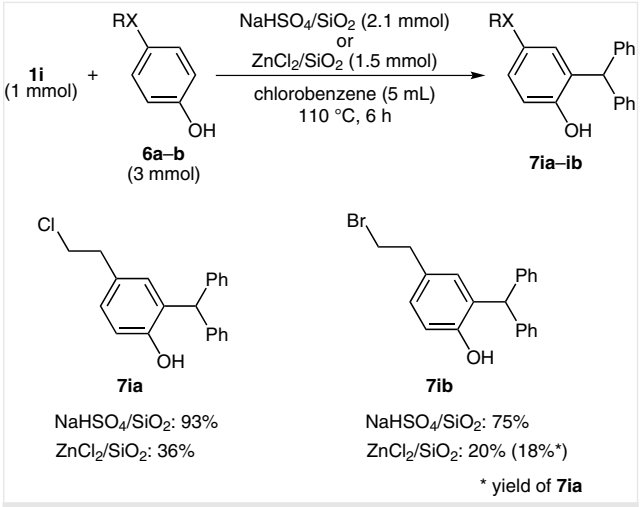
To investigate the competition between dehydrobromination and alkylation under harsh reaction conditions, we examined the reactions of 2-(2-bromoethyl)phenol (**6b**) with diones **1o**, **1q**, and **1s** in the presence of sodium bisulfate/silica gel. In the reactions of **1o** and **1q**, normal alkylation took place, but a higher temperature and larger amounts of sodium bisulfate/silica gel were needed for the complete consumption of the starting materials (Figure 1).

In the presence of sodium bisulfate/silica gel, the reaction of dione **1i** with 1-(2-bromopropyl)-4-methoxybenzene (**6c**), which has secondary alkyl bromide moiety on the ring, gave the alkylation product **7ic** in 72% yield. In contrast, when the reaction was carried out in the presence of zinc(II) chloride/silica gel, the indane derivative **8** was obtained in low yield instead of **7ic** (Scheme 12).

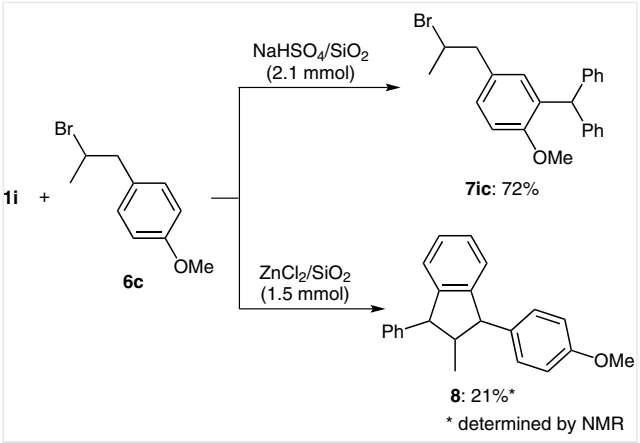
A plausible pathway for the formation of **8** is shown in Scheme 13. The zinc(II) chloride has two functions. First, it catalyzes the enolization of dione **1i** to give complex **1′**. Secondly, it eliminates bromine from bromide **6c** to form carbocation **6′**, which leads to olefin **6″**. The diphenylmethyl cation **1′** adds to olefin **6″** to give **8′**, which undergoes intramolecular cyclization to give the final product **8**.



Scheme 10



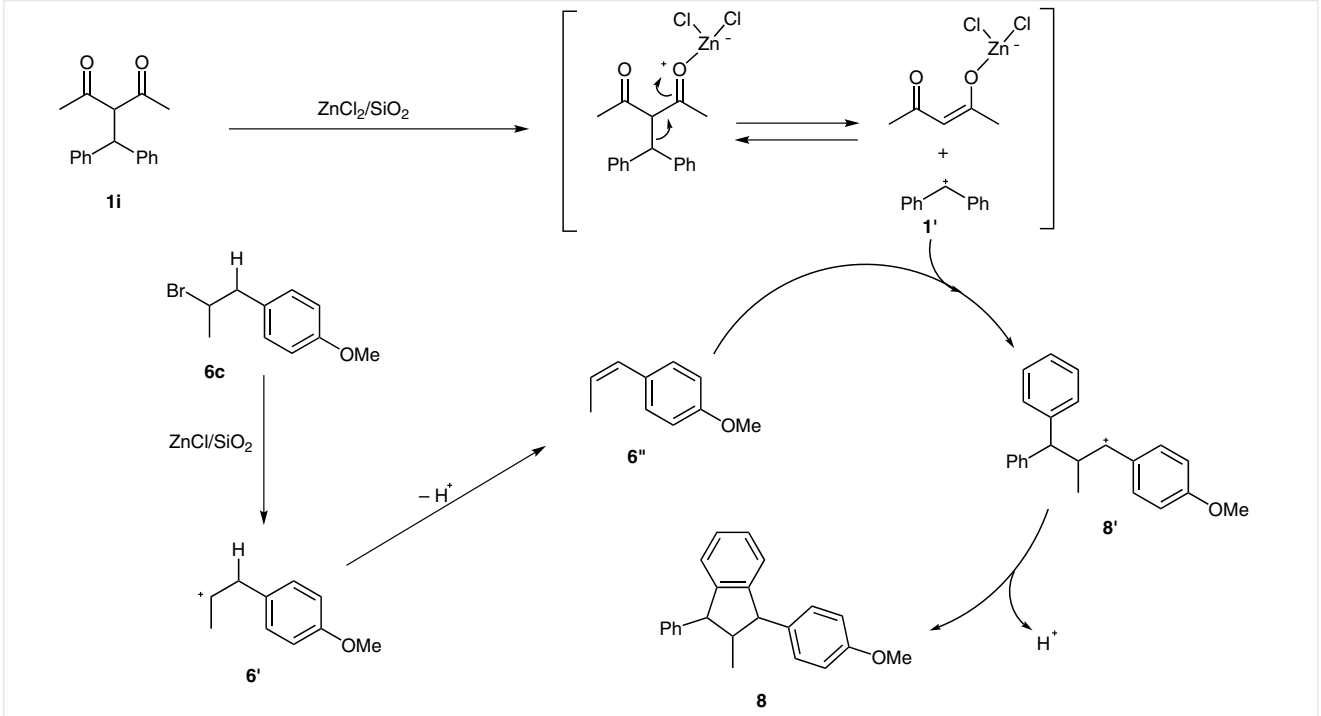
Scheme 11



Scheme 12

In conclusion, we have developed a convenient and efficient method for activating sp^2–sp^3 and sp^3–sp^3 C–C bond in 2-substituted 1,3-diketones. Both deacetylation and debenzoylation of 2-substituted 2-bromo-1,3-diketones readily occurred through cleavage of an sp^2–sp^3 C–C bond in the presence of SSA. This deacylation of 2-substituted 2-bromo-1,3-diketones was used in one-pot tandem bromination/deacylation reactions. On the other hand, when an sp^3–sp^3 C–C bond was activated in the presence of an aromatic compound with the aid of a Lewis or Brønstead acid, alkylation of the aromatic compound occurred. A significant advantage of our method is that aromatics having ω-bromoalkyl groups can be alkylated without elimination of bromine atoms.

Melting points were determined on a Yanako micro-melting point apparatus or on a Büchi Melting Point B-540. NMR spectra were recorded on a JEOL JNM-GX400 or JNM-ECX400 spectrometer; TMS (δ = 0) and $CDCl_3$ (δ = 77.0) were used as internal standards for ^1H and ^{13}C NMR, respectively. Mass analyses were performed on a Shimazu



Scheme 13

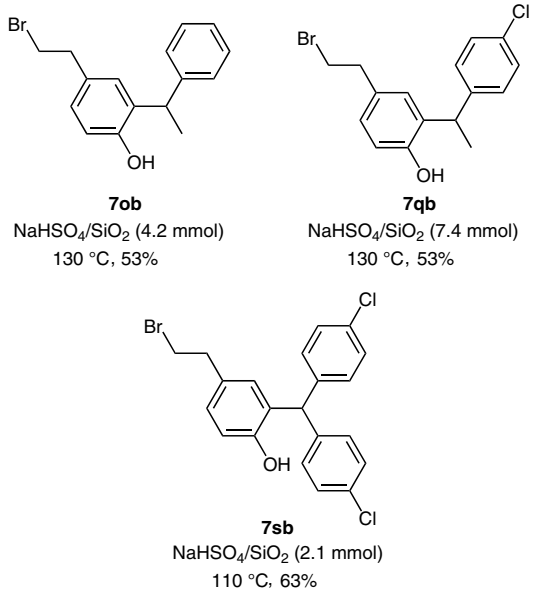


Figure 1

GCMS-QP2010 or on a JMS-GCmate (JEOL). Elemental analyses were performed on a J-Science Lab Micro Corder JM-10. IR spectra were recorded on a Thermo Electron Nicolet 380 spectrometer.

Silica Sulfuric Acid (SSA)

Silica gel [Wakogel C-200 (Wako Pure Chemical), 10.0 g], previously dried in vacuo at 120 °C for 2 h, was added to dried $CHCl_3$ (50 mL), and the mixture was stirred for 1 h. A solution of HSO_3Cl (33.3 mmol, 3.86 g) in $CHCl_3$ (50 mL) was added, and the mixture was stirred for a further 10 min. The $CHCl_3$ was removed by decantation, and the solid was washed with $CHCl_3$ (3 × 50 mL). The resulting solid was dried in vacuo at 120 °C for 2 h. Elemental analysis (found: S, 5.94%) gave an estimated sulfonic acid content of 1.85 mmol/g.

Sodium Bisulfate/Silica Gel

Silica gel (Wakogel C-200, 10.0 g) was added to a solution of $NaHSO_4{\cdot}H_2O$ (30 mmol, 4.14 g) in distilled H_2O (100 mL), and the mixture was stirred at r.t. for 0.5 h. The H_2O was removed on a rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at 120 °C for 5 h.

Zinc(II) Chloride/Silica Gel

Silica gel (Wakogel C-200, 15.9 g) was added to a solution of $ZnCl_2$ (30 mmol, 4.1 g) in distilled H_2O (100 mL), and the mixture was stirred at r.t. for 0.5 h. The H_2O was removed on a rotary evaporator under reduced pressure, and the resulting reagent was dried in vacuo (10 mmHg) at 150 °C for 6 h.

Bromo Ketones 2; General Procedure

A mixture of the appropriate diketone **1** (1 mmol) and SSA (1 g) in DCE (10 mL) was stirred at 60 °C for 1 h, and then the SSA was removed by filtration. The filtrate was evaporated to afford give corresponding product with a purity of >98%.

3-Bromo-5-phenylpentan-2-one (2b)

Colorless oil; yield: 0.186 g (77%).

IR (neat): 1716 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.36 (m, 2 H), 2.34 (s, 3 H), 2.68–2.75 (m, 1 H), 2.80–2.87 (m, 1 H), 4.17 (dd, *J* = 8.6, 5.7 Hz, 1 H), 7.19–7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6, 33.2, 34.9, 53.4, 126.3, 128.4, 128.5, 139.8, 201.5.

MS (CI): *m/z* = 241 $[M + H]^+$, 243 $[M + H + 2]^+$.

3,8-Dibromooctan-2-one (2e)

Colorless oil; yield: 0.269 g (94%).

IR (neat): 1720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.55 (m, 4 H), 1.84–2.09 (m, 4 H), 2.37 (s, 3 H), 3.41 (t, *J* = 6.8 Hz, 2 H), 4.24 (dd, *J* = 6.3, 8.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 26.4, 27.4, 32.3, 33.2, 33.5, 54.0, 201.9.

MS (CI): *m/z* = 285 $[M + H]^+$, 287 $[M + H + 2]^+$, 289 $[M + H + 4]^+$.

1-Bromo-1-phenylacetone (2g)[21]

Yellow oil; yield: 0.213 g (99%).

IR (neat): 1733 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.31 (s, 3 H), 5.43 (s, 1 H), 7.36–7.45 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 56.3, 128.7, 129.0, 129.2, 135.1, 199.3.

MS (EI): *m/z* = 212 $[M^+]$, 214 $[M + 2]^+$.

2-Bromo-1,3-diphenylpropan-1-one (2j)[22]

White solid; yield: 0.282 g (98%).

IR (neat): 1674 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (dd, *J* = 14.2, 7.3 Hz, 1 H), 3.67 (dd, *J* = 14.2, 7.3 Hz, 1 H), 5.32 (t, *J* = 7.3 Hz, 1 H), 7.25–7.30 (m, 5 H), 7.43–7.48 (m, 2 H), 7.55–7.59 (m, 1 H), 7.95–7.99 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.5, 46.6, 127.1, 128.5, 128.6, 128.8, 128.8, 129.4, 130.2, 133.7, 192.8.

MS (CI): *m/z* = 289 $[M + H]^+$, 291 $[M + H + 2]^+$.

2-Bromo-1-phenyldecan-1-one (2n)

Colorless oil; yield: 0.298 g (99%).

IR (neat): 1689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.1 Hz, 3 H), 1.27–1.58 (m, 12 H), 2.07–2.22 (m, 2 H), 5.14 (dd, *J* = 7.8, 6.9 Hz, 1 H), 7.47–7.51 (m, 2 H), 7.58–7.62 (m, 1 H), 8.01–8.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 27.5, 29.1, 29.2, 29.3, 31.8, 33.5, 47.3, 128.8, 128.8, 133.6, 134.5, 193.3.

MS (CI): *m/z* = 311 $[M + H]^+$, 313 $[M + H + 2]^+$.

Alkylated Aromatic Products; General Procedure

A mixture of diketone **1** (1.0 mmol), aromatic **3** (3.0 mmol), and $NaHSO_4/SiO_2$ (2.1 mmol/g, 1.00 g) in PhCl (5 mL) was stirred at 110 °C for 6 h. The $NaHSO_4/SiO_2$ was removed by filtration, and the filtrate was evaporated to give a crude product that was purified by column chromatography (hexane–EtOAc).

4-Chloro-2-(diphenylmethyl)phenol (4iq)

Colorless oil; yield: 0.245 g (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (s, 1 H), 5.67 (s, 1 H), 6.68 (dd, *J* = 7.1, 2.5 Hz, 1 H), 6.77 (d, *J* = 2.5 Hz, 1 H), 7.06–7.12 (m, 5 H), 7.21–7.32 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.73, 117.3, 125.7, 126.9, 127.7, 128.7, 129.2, 130.2, 132.2, 141.6, 152.0.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{19}H_{15}OCl$: 294.0811; found: 294.0809.

2-(Diphenylmethyl)-4-nitrophenol (4ir)

Yellow solid; yield: 0.092 g (30%); mp 254–257 °C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 1 H), 6.89 (d, *J* = 8.9 Hz, 1 H), 7.12–7.14 (m, 4 H), 7.27–7.37 (m, 7 H), 7.77 (d, *J* = 2.8 Hz, 1 H), 8.07 (dd, *J* = 8.9, 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.6, 116.1, 124.4, 126.5, 127.3, 128.9, 129.2, 131.5, 141.0, 141.7, 159.2.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{19}H_{15}NO_3$: 305.1052; found: 305.1054.

Anal. Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.89; H, 4.83; N, 4.51.

3-(Diphenylmethyl)-4-hydroxybenzaldehyde (4is)

White solid; yield: 0.074 g (26%); mp 231–233 °C.

^{1}H NMR (400 MHz, DMSO): δ = 5.83 (s, 1 H), 7.00 (d, *J* = 8.2 Hz, 1 H), 7.06–7.08 (m, 4 H), 7.20–7.33 (m, 7 H), 7.68 (dd, *J* = 8.2, 2.3 Hz, 1 H), 9.69 (s, 1 H), 10.8 (s, 1 H).

^{13}C NMR (100 MHz, DMSO): δ = 49.1, 115.4, 126.3, 128.0, 128.4, 129.0, 130.6, 131.2, 142.9, 160.9, 191.1.

HRMS (CI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{17}O_2$: 289.1223; found: 289.1221.

4-[1-(4-Methoxyphenyl)ethyl]benzene-1,2-diol (4pi)

White solid; yield: 0.090 g (37%); mp 116–118 °C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 7.1 Hz, 3 H), 3.78 (s, 3 H), 3.99 (q, *J* = 7.1 Hz, 1 H), 5.01 (s, 1 H), 5.07 (s, 1 H), 6.66 (dd, *J* = 7.9, 2.0 Hz, 1 H), 6.69 (d, *J* = 2.0 Hz, 1 H), 6.77 (d, *J* = 7.9 Hz, 1 H), 6.80–6.84 (m, 2 H), 7.10–7.13 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 43.2, 55.2, 113.7, 114.7, 115.1, 119.9, 128.4, 138.7, 140.2, 141.4, 143.2, 157.7.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{15}H_{16}O_3$: 244.1099; found: 244.1096.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.61; H, 6.70.

4-[Bis(4-methoxyphenyl)methyl]benzene-1,2-diol (4ri)

Red oil; yield: 0.226 g (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 6 H), 5.15 (s, 1 H), 5.17 (s, 1 H), 5.33 (s, 1 H), 6.54 (dd, *J* = 8.0, 2.3 Hz, 1 H), 6.57 (d, *J* = 2.3 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.79–6.82 (m, 4 H), 6.98–7.01 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.4, 55.2, 113.6, 115.1, 116.4, 121.9, 130.2, 136.6, 137.8, 141.8, 143.1, 157.9.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{21}H_{20}O_4$: 336.1361; found: 336.1364.

4-[Bis(4-chlorophenyl)methyl]benzene-1,2-diol (4si)

White solid; yield: 0.200 g (57%); mp 138–139 °C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.10 (s, 2 H), 5.36 (s, 1 H), 6.50 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.55 (d, *J* = 2.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 8.2 Hz, 4 H), 7.25 (d, *J* = 8.2 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.7, 115.3, 116.3, 121.9, 128.5, 130.6, 132.3, 136.1, 142.0, 142.1, 143.4.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{19}H_{14}O_2Cl_2$: 344.0371; found: 344.0371.

Anal. Calcd for $C_{19}H_{14}O_2Cl_2$: C, 66.10; H, 4.09. Found: C, 66.14; H, 3.95.

4-[(4-Methoxyphenyl)(phenyl)methyl]benzene-1,2-diol (4ti)

White solid; yield: 0.203 g (66%); mp 108–109 °C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 5.03 (s, 1 H), 5.06 (s, 1 H), 5.38 (s, 1 H), 6.55 (dd, *J* = 8.2, 2.0 Hz, 1 H), 6.59 (d, *J* = 2.0 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.80–6.83 (m, 2 H), 7.00–7.29 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (overlap), 113.6, 115.1, 116.5, 122.0, 126.2, 128.3, 129.3, 130.3, 136.2, 137.5, 141.8, 143.1, 144.3, 157.9.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{20}H_{18}O_3$: 306.1256; found: 306.1252.

4-[(4-Chlorophenyl)(phenyl)methyl]benzene-1,2-diol (4ui)

White solid; yield: 0.218 g (70%); mp 135–136 °C (hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.03 (s, 1 H), 5.05 (s, 1 H), 5.40 (s, 1 H), 6.52 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.57 (d, *J* = 2.0 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 7.01–7.08 (m, 4 H), 7.21–7.30 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 115.3, 116.5, 122.0, 126.5, 128.4 (overlap), 129.3, 130.7, 132.1, 136.6, 142.0, 142.5, 143.2, 143.5.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{19}H_{15}O_2Cl$: 310.0761; found: 310.0760.

Anal. Calcd for $C_{19}H_{15}O_2Cl$: C, 73.43; H, 4.86. Found: C, 73.53; H, 4.71.

4,4-Bis(4-chlorophenyl)butan-2-one (2s)

Colorless oil; yield: 0.049 g (17%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3 H), 3.13 (d, *J* = 7.6 Hz, 2 H), 4.56 (t, *J* = 7.6 Hz, 1 H), 7.10–7.13 (m, 4 H), 7.23–7.26 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7, 44.5, 49.3, 128.8, 129.0, 132.4, 141.9, 206.0.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{16}H_{14}OCl_2$: 292.0422; found: 292.0422.

Anal. Calcd for $C_{16}H_{14}OCCl_2$: C, 65.55; H, 4.81. Found: C, 65.36; H, 4.84.

4-(2-Bromoethyl)-2-[1-(4-chlorophenyl)ethyl]phenol (7qb)

Colorless oil; yield: 0.180 g (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58 (d, *J* = 7.1 Hz, 3 H), 3.07 (t, *J* = 7.6 Hz, 2 H), 3.50 (t, *J* = 7.6 Hz, 2 H), 4.36 (q, *J* = 7.1 Hz, 1 H), 4.74 (s, 1 H), 6.64 (d, *J* = 8.0 Hz, 1 H), 6.93 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.01 (d, *J* = 1.8 Hz, 1 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 33.5, 37.7, 38.7, 115.8, 127.6, 128.2, 128.5, 128.9, 131.3, 131.8, 131.8, 143.9, 151.9.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{16}H_{16}OBrCl$: 338.0073; found: 338.0069.

2-[Bis(4-chlorophenyl)methyl]-4-(2-bromoethyl)phenol (7sb)

White solid; yield: 0.279 g (63%); mp 103–104.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.99 (t, *J* = 7.6 Hz, 2 H), 3.44 (t, *J* = 7.6 Hz, 2 H), 4.62 (s, 1 H), 5.72 (s, 1 H), 6.59 (d, *J* = 2.3 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.99 (dd, *J* = 8.0, 2.3 Hz, 1 H), 7.01–7.04 (m, 4 H), 7.26–7.29 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.6, 38.5, 49.1, 116.0, 128.3, 128.7, 129.7, 130.6 (overlap), 131.4, 132.6, 140.8, 152.0.

HRMS (EI): *m/z* [M$^+$] calcd for $C_{21}H_{17}OBrCl_2$: 433.9840; found: 433.9839.

Anal. Calcd for $C_{21}H_{17}OBrCl_2$: C, 57.83; H, 3.93. Found: C, 57.94; H, 4.09.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378862.

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