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Synthetic Methods

An Efficient and General Iron-Catalyzed C−C Bond Activation with 1,3-Dicarbonyl Units as a Leaving Groups**

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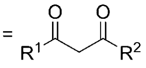
The substitution reaction is one of the fundamental reactions in chemistry and is widely applied in synthesis. Usually, a polarized and labile leaving group (LG), such as halides, tosylate, or psedohalides, is required for the success of a substitution reaction (Scheme 1). Recently, the use of carbon-based leaving groups through C−C bond cleavage has emerged as an attractive alternative in organic synthesis.[1] Three general strategies have been extensively studied: 1) the releasing of strain energy,[2] 2) cleavage of a C−C bond adjacent to carbonyl,[3] cyano,[4] carboxylic acid,[5] or hydroxy groups,[6] and 3) chelation assistance.[7] The discovery of new processes used to cleave unstrained C−C bonds still remain a major challenge.[8] Herein, we disclose the first method that uses a 1,3-dicarbonyl unit as a leaving group in a substitution reaction catalyzed by $FeCl_3$ (Scheme 1). We also demonstrate that this new strategy complements the traditional Friedel–Crafts reaction and can find application in the synthesis of indene derivatives.

$$\text{C−LG} + \text{Y} \longrightarrow \text{C−Y} + \text{LG}$$

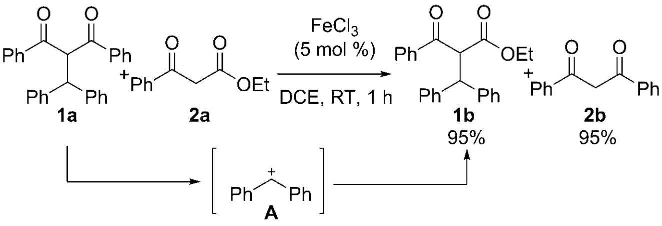
LG = halide, OTs, B, Sn, Si, metal, etc.

here LG =



Scheme 1. The 1,3-dicarbonyl units as a leaving group. Ts = 4-toluenesulfonyl, Y = nucleophile or electrophile.

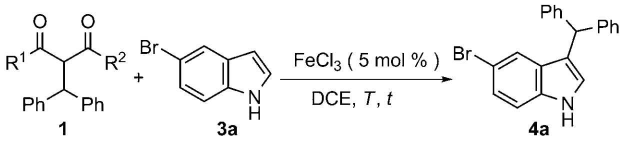
In the course of developing iron-catalyzed reactions,[9,10] we unexpectedly observed that in the presence of catalytic amount of $FeCl_3$, 2-benzhydryl-1,3-diphenylpropane-1,3-dione **1a** and ethyl 2-benzhydryl-3-oxo-3-phenylpropanoate **2a** underwent a clean exchange reaction[11] to give **1b** and **2b** (Scheme 2). We hypothesize that this reaction proceeds through a $FeCl_3$-assisted dissociation of the dicarbonyl–iron complex to give a carbocation intermediate **A** or its equivalents,[12] which can then be trapped by **2a** to give **1b** or by **2b** to give **1a**.

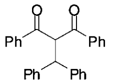
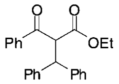
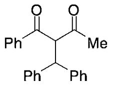
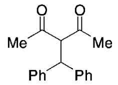
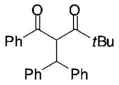
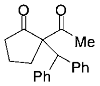


Scheme 2. Iron-catalyzed C−C bond cleavage. DCE = 1,2,-dichloroethane.

We realized that this reaction can be regarded as a substitution reaction and the 1,3-dicarbonyl functionality as a leaving group. The intermediate generated in this reaction could be the free cation **A** (S_N1-type mechanism) or an ion pair. We envisioned that if a different nucleophile is introduced, a new substitution reaction can be achieved. To this end, we had to firstly test for the best dicarbonyl leaving group (Table 1). The desired product **4a** was obtained in 93% yield when **1a** was used (Table 1, entry 1).[13] Meanwhil, β-keto ester substrate **1b** gave much lower yields of **4a** (Table 1, entries 2 and 3). Both **1c** and **1d** were less effective substrates, even at higher temperature (Table 1, entries 4 and 5).

Table 1: The reaction of diones **1** with 5-bromoindole **3a**.[a]



Entry	Dione **1**		T [°C]	t [h]	Yield [%][b]
1	**1a**		25	1	93
2	**1b**		25	3	trace
3			50	3	10
4	**1c**		50	3	15
5	**1d**		50	3	trace
6	**1e**		50	24	90
7	**1f**		50	24	33

[a] Reaction conditions: **1** (0.2 mmol), **3a** (0.2 mmol), $FeCl_3$ (0.01 mmol), DCE (5.0 mL). [b] Yield of isolated product.

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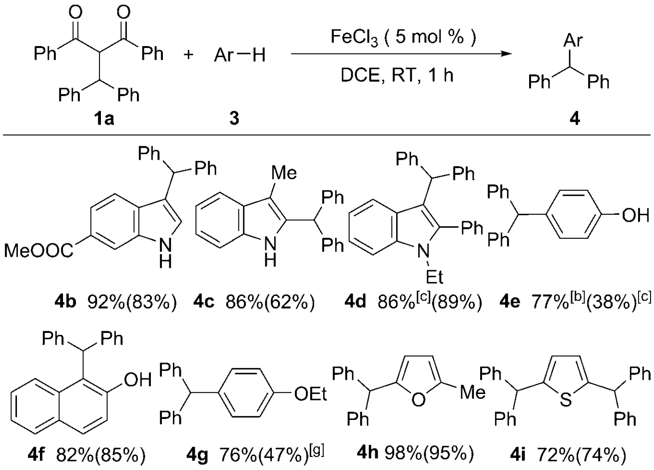
Although *tert*-butyl substrate **1e** afforded **4a** in a 90% yield, high temperature had to be applied (Table 1, entry 6). Tertiary 1,3-dicarbonyl substrate **1f** was also treated with **3a** to give the desired product **4a**, albeit in a 33% yield (Table 1, entry 7). These results indicate that a large dipole moment and bulky substituents on the 1,3-dicarbonyl group assist the present C−C bond cleavage. In other words, the efficiency of the substitution reaction depends on the thermodynamic stability of **1**.

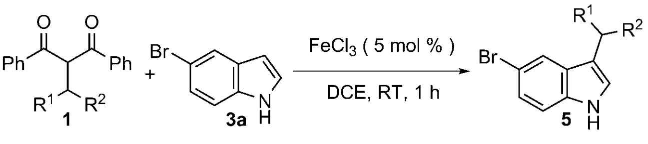
Subsequently, the scope of aromatic compounds was investigated for the present iron-catalyzed C−C bond cleavage. A variety of aromatic compounds **3** were effectively transformed into the corresponding products **4** when **1a** was used as the model substrate (Scheme 3).[14] The desired indole products **4b**–**4d** were obtained with good yields. A slightly low yield of **4e** was obtained as a result of the formation of a dialkylation phenol product. β-Naphthenol led to α-alkylation product **4f** in good yield. Other electron-rich aromatic compounds were also effective substrates in the present transformation. Even though dialkylation thiophene **4i** instead of the monoalkylation product was selectively generated. Friedel–Crafts reactions of aromatic compounds with alkyl halides or alcohols in the presence of Lewis acid are widely used. However, these reactions generally suffer from a lack of regioselectivity and low efficiency.[14b,c] In light of this, the reactions using diphenylmethanol as the alkylation reagent were also investigated (Table 2). Based on comparison, our present method shows higher efficiency (such as with **4b** and **4c**) and excellent selectivity (such as with **4e** and **4g**).

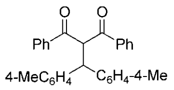
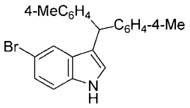
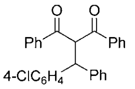
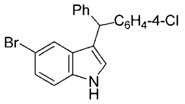
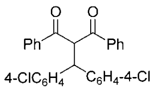
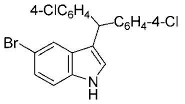
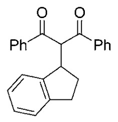
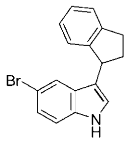
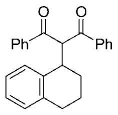
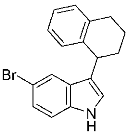
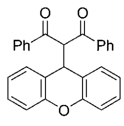
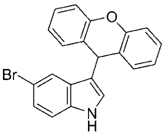
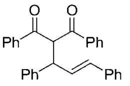
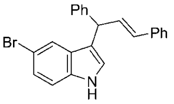
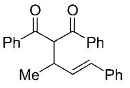
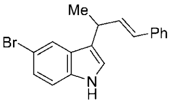
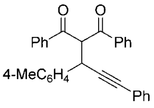
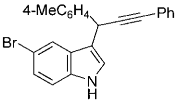
The variation of diones **1** was also examined using 5-bromoindole **3a** as a model substrate (Table 2). An electron-donating group on the phenyl ring facilitated the reaction (Table 2, entry 1). Although an electron-withdrawing group lowered the efficiency of the transformation at room temperature, **5b** and **5c** were obtained with 98% and 76% yields at 50°C, respectively (Table 2, entries 2 and 3). Cyclic substrates afforded the desired products **5d**–**5f** smoothly (Table 2, entries 4–6). Importantly, allyl 1,3-dicarbonyl substrates also gave the corresponding products (Table 2, entries 7 and 8). Product **5h** was selectively obtained under the present reaction conditions (Table 2, entry 8).[15] Moreover, alkynyl substrate **1o** was efficiently transformed into the desired product **5i** (Table 2, entry 9). To demonstrate that our substitution reaction is complementary to the classical Friedel–Crafts reaction, we examined the reaction of **6** and **3a** using 5 mol% of $FeCl_3$. In this case, the Friedel–Crafts reaction gave a mixture of **5f**, **7**, and **8**[16] [Eq. (1)]. This outcome is dramatically different from our reaction shown in Table 2, entry 6.



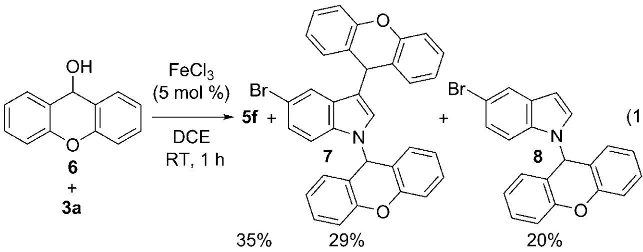
Scheme 3. The reaction of **1a** with aromatic compounds **3**. Reaction conditions: **1a** (0.2 mmol), **3** (0.2 mmol), $FeCl_3$ (5 mol%), DCE (5.0 mL), RT, 1 h. Yield for when diphenylmethanol was used instead of **1a**. The yield in parentheses for when **4** was used. [a] $FeCl_3$ (10 mol%), 50°C, 24 h. [b] 2,4-Dialkylation product **4e′** was obtained in 5% yield. [c] **4e′** was obtained in 38% yield. [d] 2,4-Dialkylation product **4g′** was obtained in 46% yield.

Table 2: The reaction of diones **1** with 5-bromoindole **3a**.[a]



Entry	Dione 1		Product 5		Yield [%][b]
1	**1g**		**5a**		95
2[c]	**1h**		**5b**		98
3[d]	**1i**		**5c**		76
4[c]	**1j**		**5d**		83
5[c]	**1k**		**5e**		92
6	**1l**		**5f**		80
7	**1m**		**5g**		73
8	**1n**		**5h**		90
9	**1o**		**5i**		96

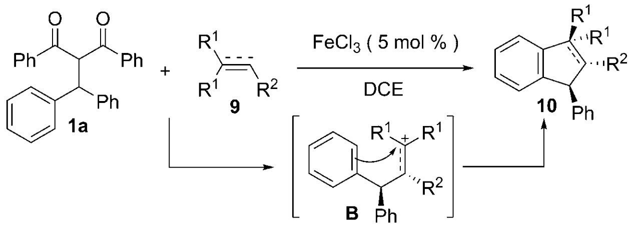
[a] Reaction conditions: **1** (0.2 mmol), **3a** (0.2 mmol), $FeCl_3$ (0.01 mmol), DCE (5.0 mL), 25°C, 1 h. [b] Yield of isolated product. [c] 50°C, 1 h. [d] 50°C, 24 h.

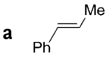
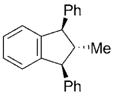
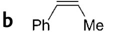
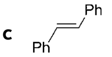
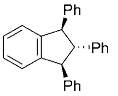
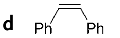
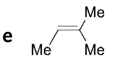
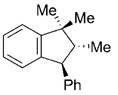
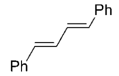
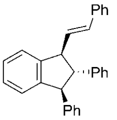
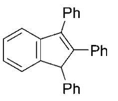
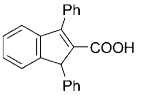
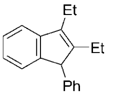


(1)

We further demonstrated the generality of our synthesis by applying this strategy in the synthesis of indene derivatives (Table 3). Although several methods have been developed for the preparation of dihydroindenes,[17] an efficient and selective method is still valuable to overcome the limitations of known methods; such as the lack of stereoselectivity and low efficiency. Both *trans*- and *cis*-β-methylstyrene (**9a** and **9b**) afforded exclusively one single dihydroindene isomer **10a** with quantitative yields (Table 3, entries 1 and 2). The stereoselectivity of this reaction is in sharply contrast with the $SnCl_4$-promoted reaction of diphenylmethanol with **9a**, for which two epimers were obtained with a 1:1.3 ratio.[17a] *trans*-Stilbene **9c** and *cis*-stilbene **9d** also gave only one epimer **10b**, however, *cis*-stilbene **9d** showed lower reactivity (Table 3, entries 3 and 4). These results indicate that the cyclization proceeds in a stepwise manner via the cationic intermediate **B** and affords the thermodynamically most stable product. Trisubstituted alkenes also worked well under the present conditions (Table 3, entry 5). Meanwhile, 2,3-dimethylbut-2-ene did not react with **1a** because of steric effects. Diene **9f** led to the corresponding product **10d** in 93 % yield (Table 3, entry 6). Furthermore, indene derivatives **10e**–**10g** were formed in moderate yields when alkyne substrates were used (Table 3, entries 7–9). The desired product **10g** was obtained by the treatment of 3-hexyne with **1a**, albeit with a low yield (Table 3, entry 9). Interesting, a 24 % yield of the dibenzylmethylation product **10g′** was also formed in this case. We hypothesized that the electron-rich properties of **10g** further reacted with the dibenzylmethyl cation that was generated in situ.

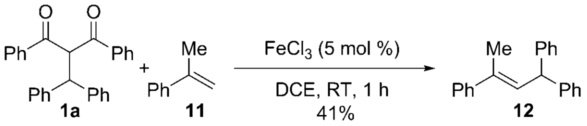
Table 3: The reaction of **1a** with alkenes and alkynes **9**.[a]



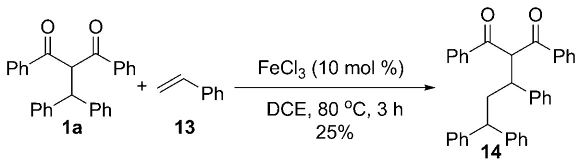
Entry	Alkene/alkyne **9**	*T*/*t* [°C/h]	Product **10**	Yield [%][b]
1	**9a** 	50/3	**10a** 	99
2	**9b** 	50/3	**10a**	99
3[c]	**9c** 	50/3	**10b** 	85
4[c]	**9d** 	50/24	**10b**	61
5	**9e** 	50/8	**10c** 	89
6	**9f** 	50/1	**10d** 	93
7[c]	**9g** $Ph-C\equiv C-Ph$	80/1	**10e** 	80
8[c]	**9h** $Ph-C\equiv C-COOH$	80/24	**10f** 	60
9[c]	**9i** $Et-C\equiv C-Et$	80/1	**10g** 	32[d]

[a] Recation conditions: **1a** (0.2 mmol), **9** (0.4 mmol), $FeCl_3$ (0.01 mmol), DCE (5.0 mL). [b] Yield of isolated product. [c] $FeCl_3$ (10 mol %). [d] Dibenzylmethyl product **10g′** was obtained in 24 % yield.

It should be noted that β-alkylation product **12** was obtained as a major product in 41 % yield when α-methylstyrene **11** was used [Eq. (2)]. This result indicates that, in this case, β-proton elimination from the proposed intermediate **B** is faster than intramolecular electrophilic aromatic cyclization. Interestingly, styrene **13** reacted with **1a** to give a formal C–C bond insertion, C=C bond product **14** [Eq. (3)]. Generation of **14** results from the further intercepted of proposed intermediate **B** by the dicarbonyl group.



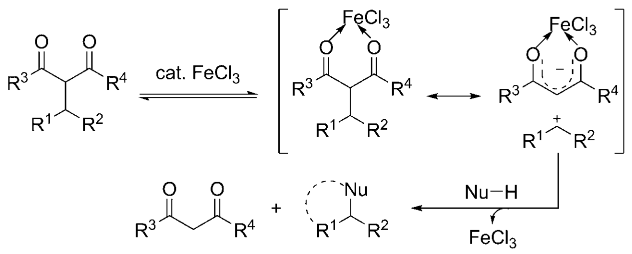
(2)



(3)

Based on the above results, a possible reaction pathway is proposed (Scheme 4). The reagent $FeCl_3$ acts as a Lewis acid catalyst to cleave a C–C bond through the coordination of iron with the 1,3-dicarbonyl unit. By taking advantage of the reversibility of the alkylation reaction of 1,3-dicarbonyl compounds, the carbocation intermediates that are generated in situ, such as **A** and **B**, are trapped by the other nucleophiles to give thermodynamically most stable alkylation products. Other possible reaction mechanisms can not be excluded at this stage and further studies on this reaction are undergoing.

In summary, we have reported a novel and efficient iron-catalyzed C–C bond cleavage under mild reaction conditions. The 1,3-dicarbonyl unit was shown to be a new and useful leaving group. The advantages of the present method include its efficiency, selectivity, and generality for organic synthesis.



Scheme 4. A tentative reaction pathway.

Furthermore, the 1,3-dicarbonyl compound could be recovered and reused. The scope, mechanism, and synthetic applications of the present reaction are under investigation.

Experimental Section

1,2-Dichloroethane (5.0 mL) was added to a mixture of **1** (0.2 mmol), **3** (0.2 mmol), and FeCl$_3$ (0.01 mmol) under nitrogen at RT. The reaction mixture was stirred at RT for 1 h. The resulting solution was quenched with saturated NaHCO$_3$ (2 mL) and extracted with dichloromethane (3×3 mL). The extract was washed with saturated NaHCO$_3$ (2×10 mL) and deionized water (10 mL) and the organic extract was dried over MgSO$_4$. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with dichloromethane/petroleum ether (1:20) as the eluent. The fraction with a $R_f = 0.6$ (dichloromethane/petroleum ether = 1:2) was collected to give the desired product **4a**. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.86$ (bs, 1H), 7.35 (d, $J = 1.6$ Hz, 1H), 7.28–7.24 (m, 4H), 7.21–7.14 (m, 8H), 6.52 (d, $J = 1.6$ Hz, 1H), 5.58 ppm (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 143.5$, 135.3, 128.9, 128.7, 128.4, 126.4, 125.2, 125.0, 122.3, 119.6, 112.7, 112.5, 48.5 ppm; ATR-FTIR: $\nu_{max} = 3425$, 3024, 2862, 1589, 1485, 1454, 1446, 1415, 1323, 1215, 1097, 1078, 1029, 918, 883, 794, 750, 729, 700, 677, 630, 582 cm^{-1}; MS (EI): *m/z* (%): 363(100), 361, 286, 284, 242, 204, 176, 165, 151, 141, 126, 102, 59, 43; HRMS calcd for C$_{21}$H$_{16}$BrNa(M+Na): 384.0358; found: 384.0360.

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