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Graphical Abstract

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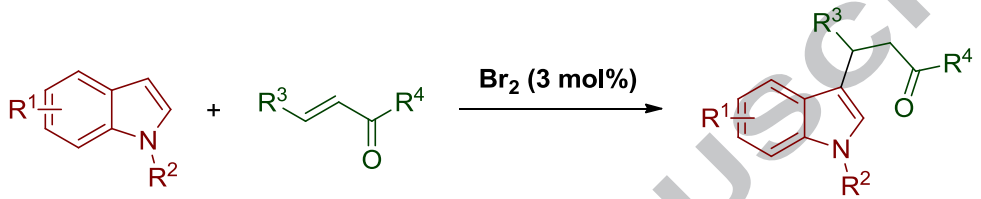

- **Unique and robust catalytic performance.**
- **Rare example of Br_2 acting as a Lewis acid catalyst.**
- **Some theoretical insights.**

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Br_2 as a novel Lewis acid catalyst for Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones

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ABSTRACT

The inexpensive Br_2 can serve as a novel Lewis acid catalyst for Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones. Under the catalysis of only 3 mol% of Br_2, this Michael addition proceeded smoothly with high efficiency and broad substrate scope. Moreover, theoretical calculations suggested that Br_2 possesses only the modest power to activate chalcones and is inferior to most tested acids, indicating that acidity might not be the primary cause for the unique activity of Br_2 in the current communication.

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Elemental bromine is essential in chemistry, and as an important member of the family of halogens, it seems to be well studied.[1] However, unlike solid molecular iodine, which has found wide applications as a catalyst in modern synthetic chemistry but is expensive,[1,2] cheap liquid bromine is underrated and found repulsive, for it is more volatile and corrosive. Elemental bromine itself has rarely been used in a catalytic manner except as an oxidant,[3] though there is an increasing tendency to explore the utility of *N*-bromosuccinimide (NBS)[4] and other solid alternatives,[5] which are associated with higher costs and/or cumbersome procedures and yet no match for molecular bromine in many cases.

We take leave to argue that chemists' distaste for bromine would only put sand in the wheels of halogen chemistry. Some time ago, HBr[6] and $CuBr_2$[7] were brought to the notice of Wang et al. for their abnormal catalytic performances in some C–C bond-forming processes, and they were claimed to depend on the nature of the counterion. On the other hand, Jamison and co-workers developed an NBS- or Br_2-catalyzed synthesis of cyclic carbonates from epoxides and CO_2, and it was pointed out that the epoxides were activated by electrophilic bromine.[8] Though in this seminal report the catalytic activity of Br_2 was not unique, it suggested that Br_2 might serve as a novel and robust Lewis acid, which was subsequently confirmed by the extremely high efficiency of Br_2 in activating aldehydes and ketones.[9] And yet for all that, the curious bromine effect is far from well understood, more and further inquiries are still needed.

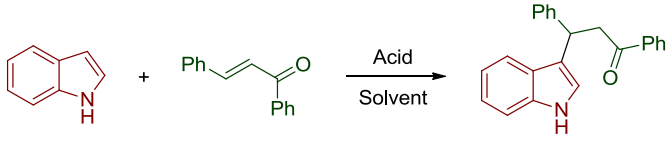
Referred to as "The Lord of the Rings" of aromatic compounds, the privileged scaffold of indole continues to fascinate chemists.[10] In this regard, β-indolylketones, generally accessed by Michael-type Friedel–Crafts (F–C) reactions of indoles with chalcones,[11,12] are versatile intermediates in organic synthesis[11b,12a,13] and building blocks for biologically active molecules.[13c] In spite of the great advances in asymmetric F–C alkylations of indoles with chalcone derivatives, which were catalyzed by dear metal complexes or other elaborated chiral acids,[11] in most cases the synthesis of β-indolylketones required rather high catalyst loading.[11,12] Hence, there is still an urgent need to develop cheaper and more powerful catalyst for this important transformation.

Inspired by the aforementioned curious bromine effect,[6-9] and in an effort to gain further insights into it, we evaluated the catalytic power of Br_2 in this F–C alkylation. Here, we present an efficient Br_2-catalyzed Michael addition reaction of indoles with simple α,β-unsaturated ketones, wherein only 3 mol% of catalyst was required, and theoretical calculations proved that Br_2 possesses only the modest power to activate chalcone, suggesting that acidity might not be the primary cause of the unique performance of Br_2.

Our studies commenced with the F–C conjugate addition between indole **1a** and chalcone **2a** (Table 1). Much to our satisfaction, in the presence of only 5 mol% of Br_2 in MeCN, the addition was completed in 2 h at 50 °C, affording dihydrochalcone **3a** in 92% yield (entry 1). While no reaction occurred after 24 h with NBS as the catalyst (entry 2), the employment of I_2 resulted in incomplete F–C alkylation even after 24 h (entry 3). HBr (40% aqueous) also proved to be an excellent catalyst for this transformation, and **3a** was delivered in an excellent yield in a longer reaction time when it was used (entry 4), whereas $CuBr_2$ was less effective for the use of it led to much longer reaction time (entry 5). It is worthy of notice that a minute quantity of water (i.e., the same amount of water contained in aqueous HBr in the same loading) hardly affected the Br_2-catalyzed addition (entry 6), and when 4 Å molecular sieves (MS) were additionally added, the reaction catalyzed by HBr was retarded (entry 7), probably due to the adsorption of the catalyst. Tetrabutyl ammonium bromide (TBAB), an established bromide ion source in Wang's work,[6a] did not show significant counterion effect here (entry 8). Although the possibility that more or less there might be HBr generated in situ by bromination of indole in the Br_2-catalyzed processes could not be ruled out,[14] the apparently superior performance of Br_2 clearly suggests that they were two independent catalysts.

Next, a survey of a range of typical Brønsted and Lewis acids was conducted. It was found that none of the tested acids was active enough to enable full conversion of **1a** even after a prolonged reaction time of 24 h, and while the employment of HI (47% aqueous, entry 9), H_2SO_4 (entry 10), TsOH (entry 11), $BF_3{\cdot}Et_2O$ (entry 13), $TiCl_4$ (entry 15), or $SnCl_4$ (entry 16) gave 3-alkylindole **3a** in relatively high yields, with trifluoroacetic acid (TFA, entry 12) or $FeCl_3$ (entry 14) as catalyst, **3a** was yielded in 14% and 50% yields, respectively. The comparison of a series of

Table 1. Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Acid (mol%)	Solvent	*T* (°C)	*t* (h)	Yield of **3a**[b] (%)
1	Br_2 (5)	MeCN	50	2.0	92
2	NBS (5)	MeCN	50	24	nr
3	I_2 (5)	MeCN	50	24	82 (12)[c]
4	HBr (5)	MeCN	50	3.5	90
5	$CuBr_2$ (5)	MeCN	50	11	87
6[d]	Br_2 (5)	MeCN	50	2.0	91
7[e]	HBr (5)	MeCN	50	24	37 (59)[c]
8[f]	Br_2 (5)	MeCN	50	2.0	93
9	HI (5)	MeCN	50	24	78 (19)[c]
10	H_2SO_4 (5)	MeCN	50	24	77 (18)[c]
11	TsOH (5)	MeCN	50	24	75 (19)[c]
12	TFA (5)	MeCN	50	24	14 (81)[c]
13	$BF_3{\cdot}Et_2O$ (5)	MeCN	50	24	73 (21)[c]
14	$FeCl_3$ (5)	MeCN	50	24	50 (46)[c]
15	$TiCl_4$ (5)	MeCN	50	24	83 (11)[c]
16	$SnCl_4$ (5)	MeCN	50	24	86 (11)[c] (32)[g]
17	Br_2 (5)	CH_2Cl_2	50	24	88 (8)[c]
18	Br_2 (5)	THF	50	24	86 (9)[c]
19	Br_2 (5)	DMF	50	24	nr
20	Br_2 (5)	EtOH	50	24	80 (13)[c]
21	Br_2 (5)	Toluene	50	24	45 (51)[c]
22	Br_2 (5)	MeCN	rt	24	82 (12)[c]
23	**Br_2 (3)**	**MeCN**	**50**	**7.0**	**93**
24	Br_2 (2)	MeCN	50	24	88 (6)[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.55 mmol), solvent (2.5 mL).

[b] Isolated yields.

[c] Recovery of **1a**.

[d] 0.003 mL H_2O was added.

[e] 200 mg 4 Å MS was added.

[f] 5 mol% of Bu_4NBr was added.

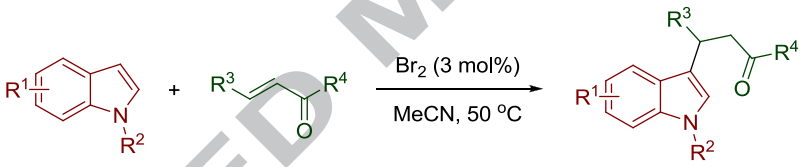
[g] The reaction was run in a sealed tube with CH_2Cl_2 as the solvent.

solvents revealed that using CH_2Cl_2 (entry 17), THF (entry 18), EtOH (entry 20) or Toluene (entry 21) as the solvent, this Br_2-catalyzed F–C alkylation did not reach completion even after 24 h, and that the use of *N*,*N*-dimethylformamide (DMF) proved unfruitful (entry 19). A high yield of 82% was still achieved when the reaction was performed at ambient temperature for 24 h (entry 22). Finally, we were pleased to find that 3 mol% of Br_2 was sufficient to make this F–C reaction complete within 7 h (entry 23), and even further reducing the catalyst loading to 2 mol%, 88% yield of **3a** was still obtained by prolonging the reaction time to 24 h (entry 24).

Having developed optimized reaction conditions (entry 23, Table 1), we subsequently explored the scope of this Michael addition reaction with respect to the indoles **1** and α,β-unsaturated ketones **2**.[15] As shown in Table 2, a broad range of chalcones **2** reacted smoothly with indole **1a** to provide the corresponding adducts **3** in high to excellent yields. Both electron-donating (entries 2 and 3) and -withdrawing substituents (entries 4-7) at the para, meta, or ortho positions of the aroyl group were compatible with this transformation. The use of 2-furoyl (entry 8) or -thenoyl (entry 9) substrates **2h,i** also provided the desired products **3h,i** in excellent yields. Unfortunately, benzylideneacetone **2j** proved to be a challenging substrate, and the reaction of it with **1a** did not yield the target adduct but an unidentified compound, the NMR spectra of which were rather complex and defied analysis (entry 10), probably due to the competitive condensation at the carbonyl carbon.[9b] Surprisingly, when dibenzylideneacetone **2k** was used, monoadduct **3j** was exclusively furnished within 2 h. Attempt to achieve double addition just by using 2 equivalents of indole **1a** met with no success, but resulted in much lower reaction rate (entry 11), probably attributed to the complexation of Br_2 by excessive **1a**.[9b] Optimized geometry at B3LYP[16]/6-31+G(d,p)[17] level illustrated that there is no substantial steric hindrance for further addition of indole **1a** to **3j** (see Figure S1), though calculations at the same level suggested that this monoadduct is thermodynamically more stable. Nevertheless, with 10 mol% of Br_2 at 80 °C, diadduct **4** was efficiently furnished in 87% yield within 5 h (Scheme 1). On the other hand, chalcones **2l-p** bearing either electron-deficient (entries 12 and 13) or -rich β-aryl ring (entries 14-16) all worked well in this F–C alkylation, affording expected products **3k-o** in high to excellent yields. In the case concerning 4-nitrochalcone **2m**, the reaction should be performed at room temperature or complex mixture would be yielded (entry 13). The addition of indole **1a** to 2-furfurylideneacetophenone **2q** also proceeded well, providing product **3p** in 79% yield (entry 17). Notably, vinyl ketone **2r** reacted smoothly with **1a** as well at 80 °C and the catalyst loading of 10 mol%, giving adduct **3q** in a high yield after 24 h (entry 18).

Then, the F–C reaction was extended to various substituted indoles **1**. Whereas 2-methylindole **1b** reacted rapidly with chalcone **2a** to furnish adduct **3r** in 96% yield within 12 min (entry 19), the reaction of electron-deficient ethyl indole-2-carboxylate **1c** needed to be carried out at 80 °C using 10 mol% of catalyst, and still, after 24 h only a moderate yield of 3-

Table 2. Michael reaction leading to adduct **3**[a]



1 **2** **3**

Entry	**1**	R^1	R^2	**2**	R^3	R^4	*t* (h)	**3**	Yield[b] (%)
1	**1a**	H	H	**2a**	Ph	Ph	7.0	**3a**	93
2	**1a**	H	H	**2b**	Ph	4-MeOPh	9.0	**3b**	91
3	**1a**	H	H	**2c**	Ph	2-MePh	14	**3c**	90
4	**1a**	H	H	**2d**	Ph	4-ClPh	10	**3d**	92
5	**1a**	H	H	**2e**	Ph	4-NO_2Ph	3.0	**3e**	92
6	**1a**	H	H	**2f**	Ph	3-NO_2Ph	4.0	**3f**	90
7	**1a**	H	H	**2g**	Ph	2-NO_2Ph	6.0	**3g**	82
8	**1a**	H	H	**2h**	Ph	2-Furyl	7.0	**3h**	91
9	**1a**	H	H	**2i**	Ph	2-Thienyl	6.0	**3i**	90
10	**1a**	H	H	**2j**	Ph	Me	5.0		nd
11	**1a**	H	H	**2k**	Ph	PhCH=CH	2.0	**3j**	81 (82)[c] (56)[d]
12	**1a**	H	H	**2l**	4-ClPh	Ph	7.0	**3k**	93
13[e]	**1a**	H	H	**2m**	4-NO_2Ph	Ph	24	**3l**	70
14	**1a**	H	H	**2n**	4-MePh	Ph	12	**3m**	84
15	**1a**	H	H	**2o**	2-MePh	Ph	8.0	**3n**	89
16	**1a**	H	H	**2p**	3,4-$(MeO)_2$Ph	Ph	6.0	**3o**	75
17	**1a**	H	H	**2q**	2-Furyl	Ph	9.0	**3p**	79
18[f]	**1a**	H	H	**2r**	H	Ph	24	**3q**	72
19	**1b**	2-Me	H	**2a**	Ph	Ph	0.2	**3r**	96
20[f]	**1c**	2-CO_2Et	H	**2a**	Ph	Ph	24	**3s**	44
21	**1d**	5-MeO	H	**2a**	Ph	Ph	7.0	**3t**	86
22	**1e**	5-Br	H	**2a**	Ph	Ph	1.0	**3u**	95
23	**1f**	5-NO_2	H	**2a**	Ph	Ph	16	**3v**	93
24	**1g**	6-Cl	H	**2a**	Ph	Ph	3.5	**3w**	88

25	**1h**	7-Me	H	**2a**	Ph	Ph	3.0	**3x**	97
26[e]	**1i**	H	Me	**2a**	Ph	Ph	0.5	**3y**	96
27[f]	**1j**	H	$PhSO_2$	**2a**	Ph	Ph	24		nr

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.55 mmol), MeCN (2.5 mL).

[b] Isolated yields.

[c] The reaction time was prolonged to 24 h.

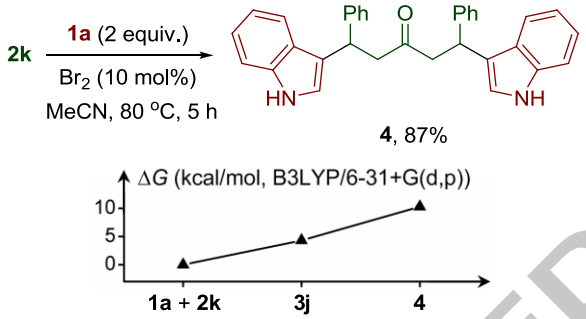
[d] The reaction was run with 2 equiv. of **1a** for 24 h.

[e] The reaction was run at room temperature.

[f] 10 mol% of Br_2 was used, and the reaction was run at 80 °C.

alkylindole **3s** was generated (entry 20). It proved that indoles **1d-h** bearing either electron-donating (entries 21 and 25) or -withdrawing groups (entries 22-24) at C(5)-C(7) were all adept in efficiently furnishing the corresponding products **3t-x** in 86-97% yields under the optimized reaction conditions. While desired dihydrochalcone **3y** was delivered rapidly from *N*-methylindole **1i** in 96% yield within 30 min just at room temperature (entry 26), when the indolic nitrogen was protected by electron-withdrawing phenylsulfonyl group, great sluggishness was observed even under those enhanced conditions (entry 27).

In an effort to gain insights into the extraordinary performance



Scheme 1. Double F–C alkylation of **2k**

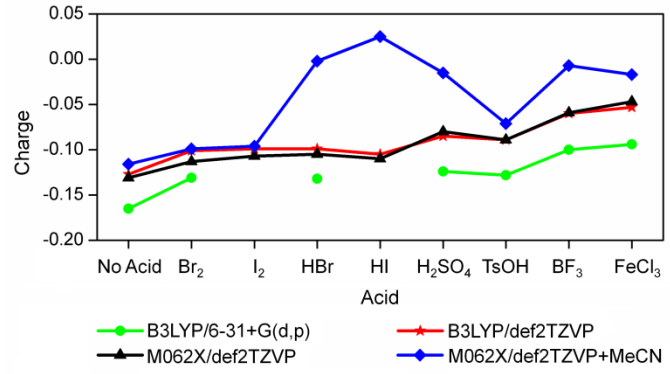


Figure 1. NBO charge distributions on the β-carbon of chalcone activated by various acids

of Br_2, theoretical calculations of the power of various electrophilic species in activating the β-carbon of chalcone **2a** were performed. Upon coordination of the carbonyl oxygen atom to them, the electron density of the β-carbon would be decreased. First, a range of Brønsted and Lewis acids were compared (Figure 1, for details see Table S1). Confusingly, natural bonding orbital (NBO) charge distributions at various levels, including B3LYP/6-31+G(d,p), B3LYP/def2TZVP,[18] and M062X[19]/def2TZVP, all suggested that most tested acids were superior to Br_2 more or less, and while the powers of HBr, HI, H_2SO_4, TsOH, BF_3, and $FeCl_3$ were further enhanced to varying degrees when the solvent effect of MeCN was considered, the ones of Br_2 and I_2 were basically unaffected (M062X/def2TZVP+MeCN[20]).

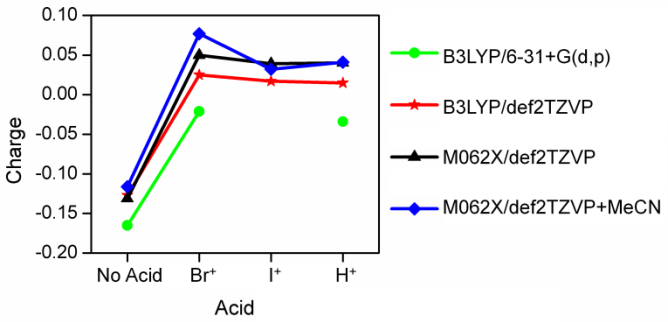


Figure 2. NBO charge distributions on the β-carbon of chalcone activated by positive ions

However, the comparison of free bromonium, iodonium, and hydrogen ions revealed that bromonium ion is more robust as a chalcone activator (Figure 2, for details see Table S1), which might be related to the high electronegativity in combination with high polarizability of the element of bromine. Thus, it appears that the true catalyst in the above reactions is more likely to be the bromonium ion. However, considering that the organic and weak-polar solvent of MeCN was the reaction medium, the electrophilic bromine was unlikely to be so free.[1] This is also supported by our calculations, which showed that in MeCN Br_2 was not significantly polarized during activation of chalcone or complexation by solvent molecules, judging by the bond lengths and NBO charge distributions (see Figure S2). As a result, we assume that in the present reaction acidity might not be the primary cause of the unique activity of Br_2, the origin of which remains unclear at this time. Further exploration still needs to be carried out.

In conclusion, we have demonstrated that Br_2 could act as a novel Lewis acid catalyst for Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones, and have developed a mild and efficient synthesis of β-indolylketone derivatives. Furthermore, theoretical calculations revealed that in terms of the ability to activate chalcones, Br_2 possesses only the modest power and is inferior to most tested Brønsted and Lewis acids, thus indicating that acidity might not be the primary cause for the remarkable activity of Br_2 presented here. This work might inspire more novel Br_2-catalyzed reactions and provide further clues for the understanding of the curious bromine effect, further studies toward which are underway in our laboratory.

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15. *General procedure for the synthesis of β-indolylketones (**3a** as an example):* To a stirred solution of indole **1a** (59 mg, 0.5 mmol) and chalcone **2a** (115 mg, 0.55 mmol) in MeCN (2.0 mL) was added a solution of Br_2 (0.00077 mL) in MeCN (0.5 mL), and the mixture was stirred for 7.0 h at 50 ℃. After **1a** was consumed, as indicated by TLC, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (0.2 mL) and water (10.0 mL), and extracted with CH_2Cl_2 three times. The residue obtained after evaporation of the solvent was purified by column chromatography on silica gel (petroleum ether–ethyl acetate = 30:1, v/v) to afford 3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-one **3a** as a white solid (151 mg, 93% yield): mp 138-139 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.69-3.85 (m, 2H), 5.07 (dd, *J* = 7.2, 7.2 Hz, 1H), 6.99-7.03 (m, 2H), 7.12-7.18 (m, 2H), 7.23-7.27 (m, 2H), 7.31-7.36 (m, 3H), 7.40-7.44 (m, 3H), 7.53 (tt, *J* = 1.3, 7.4 Hz, 1H), 7.91-7.94 (m, 2H), 7.95 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.7, 144.3, 137.1, 136.6, 133.0, 128.6, 128.5, 128.1, 127.8, 126.6, 126.3, 122.1, 121.5, 119.5, 119.4, 119.2, 111.2, 45.3, 38.3; HRMS (ESI-TOF) Calcd for $C_{23}H_{20}NO^+$ ($[M+H]^+$) 326.1539. Found 326.1537.
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Supplementary Material

Supplementary data associated with this article can be found in the online version.