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Catalytic Efficient Nazarov Reaction of Unactivated Aryl Vinyl Ketones via a Bidentate Diiron Lewis Acid Activation Strategy

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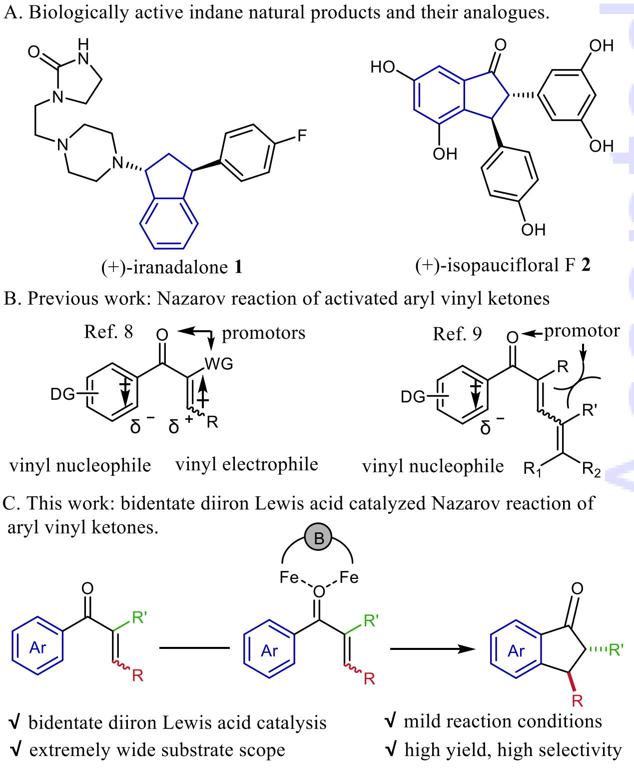
Abstract. A catalytic highly efficient Nazarov reaction of unactivated aryl vinyl ketones has been accomplished by employing aryl boric acid/Fe(OTf)$_3$. Significant progress was obtained in utilizing an extremely broad substrate scope, giving indanones in high yields with high regioselectivities and diastereoselectivities. The mechanistic investigation supports a bidentate diiron Lewis acid catalysis, and the strong double electrophilic activation of aryl vinyl ketones via simultaneous coordination plays a key role in achieving a high reaction efficiency.

Keywords: Nazarov reaction; Lewis acid catalysis; Indanone; 4π electrocyclization; aryl vinyl ketone

Indane frameworks are widely found in natural products and drug candidates possessing intriguing bioactivities (Figure 1, A).[1] Intense efforts have been devoted to their synthesis.[2] However, as theoretically one of the most efficient strategies for the synthesis of indanones, the catalytic Nazarov reaction of aryl vinyl ketones has been rarely explored due to the sluggish reactivity caused by the breaking of the aromaticity during the reaction.[3-6] Stoichiometric or superstoichiometric amounts of strong Brønsted or Lewis acids are generally required.[7] Thus far, only limited catalysts, such as Cu(II), Ir(III), Au(III) and Al(III) have been developed for the activation of aryl vinyl ketones based on the “polarizing strategy”,[8] or the steric effect (Figure 1, B).[9] Coorperative catalysis for the polarizing aryl vinyl ketones was also developed by professor Luo by using In(OTf)$_3$/phosphoric acid as the catalyst.[8d] Moreover, the effect on the aryl moiety of aryl vinyl ketones was investigated, but electron deficient moieties have been scarcely explored. These limited the utilization of Nazarov reaction of aryl vinyl ketones for the synthesis of indanones.

Lewis acids play a major role as catalysts in the contemporary organic synthesis. Bidentate Lewis acid catalysis, based on the simultaneous double coordination and activation of a single substrate, is potentially valuable since it promises to demonstrate an even higher catalytic efficiency than the respective monofunctional Lewis acid, concequently expanding the substrate scope.[10] Nevertheless, to date, relatively few examples of bidentate Lewis acid catalysis have been reported,[11] which may be caused by the difficulty of synthesis and the highly favored double coordination leading to catalyst deactivation.[10a,12] Herein, we report the bidentate diiron Lewis acid catalyzed Nazarov reaction of unactivated aryl vinyl ketones by using aryl boric acid/Fe(OTf)$_3$ (Figure 1, C). The process delivered a wide substrate scope, giving indanones in high yields with high regioselectivities and diastereoselectivities.


A. Biologically active indane natural products and their analogues.

(+)-iranadalone **1**

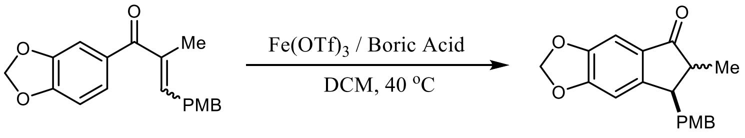
(+)-isopaucifloral F **2**

B. Previous work: Nazarov reaction of activated aryl vinyl ketones

C. This work: bidentate diiron Lewis acid catalyzed Nazarov reaction of aryl vinyl ketones.

Figure 1. Nazarov strategy for the synthesis of indanones.

Table 1. Optimization of the Reaction Conditions.



1a **2a**

Entry[a]	Lewis Acid	Boric Acid	Time [h]	Yield [%][b]
1	$Cu(OTf)_2$	None	6	0
2	$Ni(OTf)_2$	None	6	0
3	$Fe(OTf)_2$	None	6	0
4	$Sc(OTf)_3$	None	6	0
5	$Al(OTf)_3$	None	1.5	22
6	$In(OTf)_3$	None	6	37
7	$Fe(OTf)_3$	None	6	50
8	$BF_3.OEt_2$	None	6	43
9[c]	None	$3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$	6	0
10	$Al(OTf)_3$	$3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$	1.5	33
11	$In(OTf)_3$	$3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$	4	52
12	$Fe(OTf)_3$	$PhB(OH)_2$	4	47
13	$Fe(OTf)_3$	$3,5\text{-}C_6H_3F_2B(OH)_2$	4	56
14	$Fe(OTf)_3$	$C_6F_5B(OH)_2$	4	72
15	$Fe(OTf)_3$	$3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$	4	77
16	$Fe(OTf)_3$	$BF_3.OEt_2$	4	92
17[d]	$Fe(OTf)_3$	$3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$	1.5	95

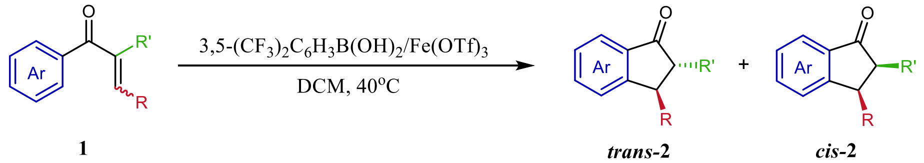
[a] Reaction conditions: 1a (0.1 mmol), $Fe(OTf)_3$ (10 mol%), boric acid (10 mol%) in DCM under N_2. [b] Yield of the isolated product. [c] Other aryl boric acids listed in table 1 were also tested, no reaction occurred. [d] Catalyst $3,5\text{-}(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ (1:2, 5 mol%) was used.

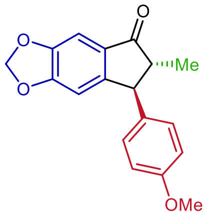
Since various Lewis acids were effective activators for boric acids,[13] it is surmised that such a complex may act as a bidentate Lewis acid, thus effectively activating the aryl vinyl ketones. Indeed, the catalytic efficiency of the reaction was improved using aryl boric acid/$Al(OTf)_3$, $In(OTf)_3$ and $Fe(OTf)_3$ (Table 1, entries 10-15 vs 5-7).[14a,15] By increasing the Lewis acidity of boric acids, the reactivity of the reaction was improved as anticipated (entries 12-15). Indanone **2a** was obtained with a 77% yield using $3,5\text{-}(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ as the catalyst (entry 15). $BF_3{\cdot}OEt_2/Fe(OTf)_3$ catalyzed the reaction more efficiently,[14b] giving the corresponding **2a** in a 92% yield (entry 16). Further investigation revealed that the ratio of aryl boric acid/$Fe(OTf)_3$ has a significant effect on the reactivity of the reaction. $3,5\text{-}(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ (1:2, 5 mol%) catalyzed the reaction smoothly, and delivered indanone **2a** in 95% yield with 10:1 d.r. favoring the *trans* stereoisomer within 1.5 hours (entry 17).[14c]

With the optimized reaction conditions in hand, we first investigated the effect of the aryl fragment of unactivated aryl vinyl ketones (Table 2, **2a-2p**). The electron rich aryl vinyl ketones underwent the reaction smoothly, giving the corresponding indanones in excellent yields with good diastereoselectivities (Table 2, **2a-2e**). It is noteworthy that aryl vinyl ketones bearing a *p*-methoxyl group on the aryl moiety also worked very well (Table 2, **2f**), which sharply contrasted with previous reports.[7e,8d] The Nazarov reaction of electron deficient aryl vinyl ketones represented a significant challenge for the synthesis of indanones, and has been scarcely investigated.[3] To our delight, $3,5\text{-}(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ (1:2) catalyzed the reaction smoothly, giving the corresponding indanones in good yields with good to excellent diastereoselectivities (Table 2, **2h-2n**). To the best of our knowledge, this was the first example of the catalytic Nazarov reaction of electron deficient aryl vinyl ketones. To further expand the substrate scope, heteroaryl vinyl ketones were tested, and excellent results were obtained (**2o-2p**).

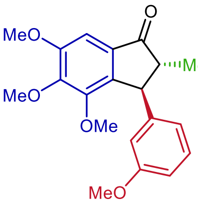
Subsequently, the influence of the vinyl fragment of aryl vinyl ketones was investigated (Table 2, **2q-2zc**). Various β-aryl (**1q-1t**), heteroaryl (**1u**) and alkyl substituted aryl vinyl ketones (**1w**) as well as aryl dienyl ketone (**1v**) underwent the reaction smoothly, providing the corresponding indanones in high yields with high diastereoselectivities (Table 2, **2q-2w**). The α-alkyl aryl vinyl ketones were also suitable substrates for the Nazarov reaction, and indanones **2x-2za** were obtained in high yields with excellent diastereoselectivities. With respect to α-aryl vinyl ketone **1zb**, however, the reaction did not proceed, which may be caused by the steric interactions. Fortunately, $BF_3{\cdot}OEt_2/Fe(OTf)_3$ (1:1, 5 mol%) could efficiently catalyze the reaction (Table 2, **2zb**).[14d] The synthetic utility of the methodology was further demonstrated by the formal synthesis of (±)-isopauciflorel F. The Nazarov reaction of **1zc** proceeded smoothly, giving indanone **2zc** in a 94% yield within 4 hours (Table 2, **2zc**). The formal synthesis of (±)-isopauciflorel F was then completed following the previous report of Professor Snyder.[2d]

Table 2. Effect of the aryl fragment of unactivated aryl vinyl ketones for the Nazarov reaction.[a]

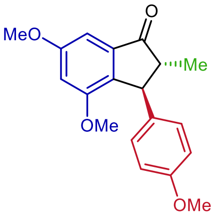




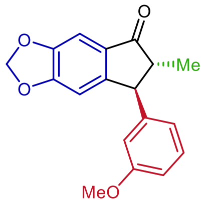
2a: 95%, 10:1 d.r.



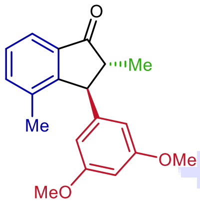
2b: 94%, 33:1 d.r.



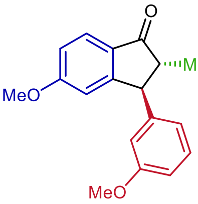
2c: 91%, 8:1 d.r.



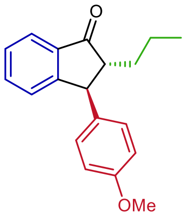
2d: 92%, 14:1 d.r.



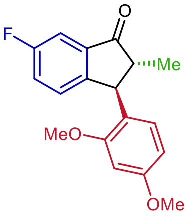
2e: 89%, 16:1 d.r.



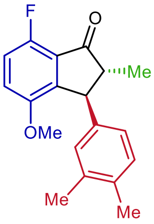
2f: 93%, 14:1 d.r.



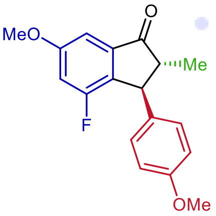
2g: 95%, 33:1 d.r.



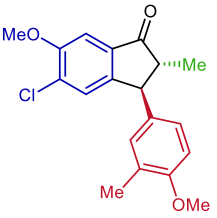
2h: 85%, 10:1 d.r.[b]



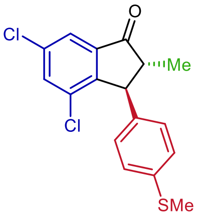
2i: 91%, 5:1 d.r.



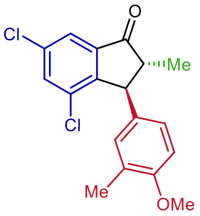
2j: 88%, 5:1 d.r.



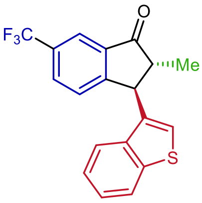
2k: 93%, 100:1 d.r.



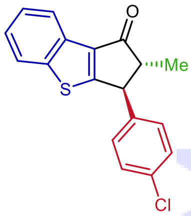
2l: 89%, 4:1 d.r.



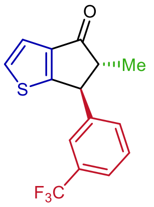
2m: 89%, 4:1 d.r.



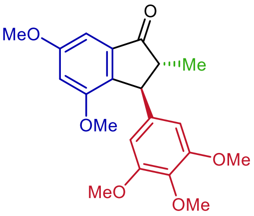
2n: 83%, 100:1 d.r.[b,c]



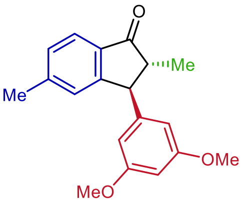
2o: 92%, 100:1 d.r.



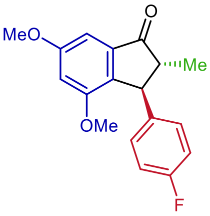
2p: 88%, 100:1 d.r.[c]



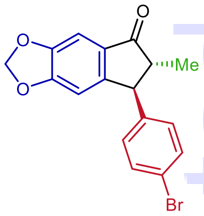
2q: 97%, 5:1 d.r



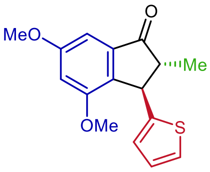
2r: 91%, 14:1 d.r



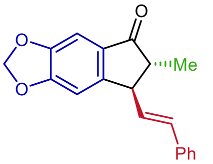
2s: 88%, 33:1 d.r



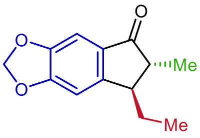
2t: 89%, >100:1 d.r



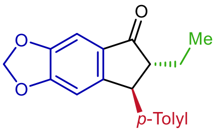
2u: 92%, 5:1 d.r



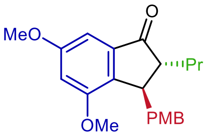
2v: 91%, >100:1 d.r



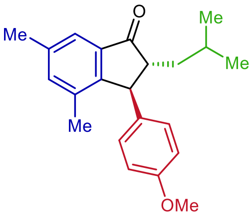
2w: 97%, 33:1 d.r



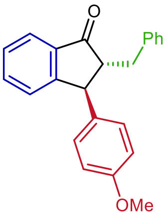
2x: 91%, 20:1 d.r



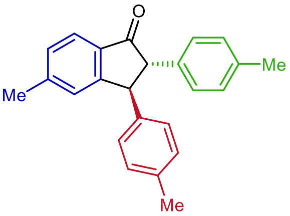
2y: 97%, 10:1 d.r



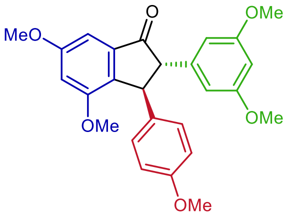
2z: 87%, 25:1 d.r



2za: 89%, 25:1 d.r



2zb: 92%, >100:1 d.r[d]



2zc: 94%, >100:1 d.r[d]
methylated (±)-isopaucifloral F

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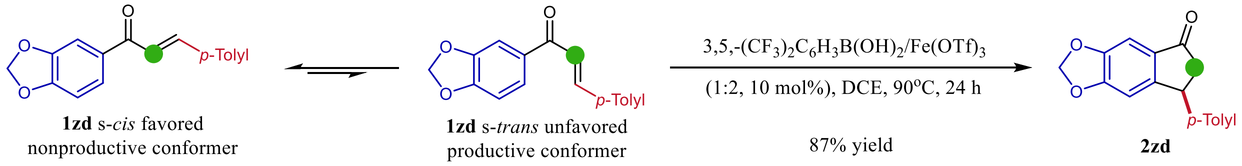
[a] Reaction conditions: 3,5-$(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ (1:2, 5 mol%), **1** (0.2 mmol), in DCM (1.0 mL) under N_2 at 40 °C. [b] Catalyst loading: 10 mol%. [c] Reaction proceeded in DCE (1.0 mL) at 70 °C. [d] Catalyst $BF_3{\cdot}OEt_2/Fe(OTf)_3$ (1:1, 5 mol%) was used.

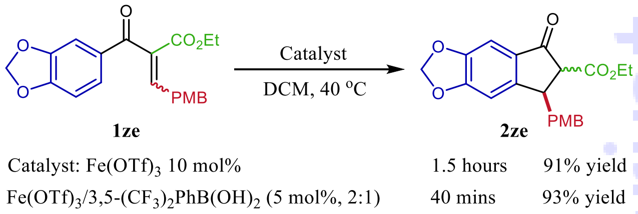


Scheme 1. Nazarov reaction of α-unsubstituted chalcone.

The α-unsubstituted chalcones represent a significant challenge for the catalytic Nazarov reaction, not only because of the inherent sluggish reactivity of aryl vinyl ketones but also because of the much favored nonproductive s-*cis* conformation.[9] To our delight, the first catalytic Nazarov reaction of α-unsubstituted chalcones was realized using our catalyst, giving indanone **2zd** in an 87% yield (Scheme 1).[14e]

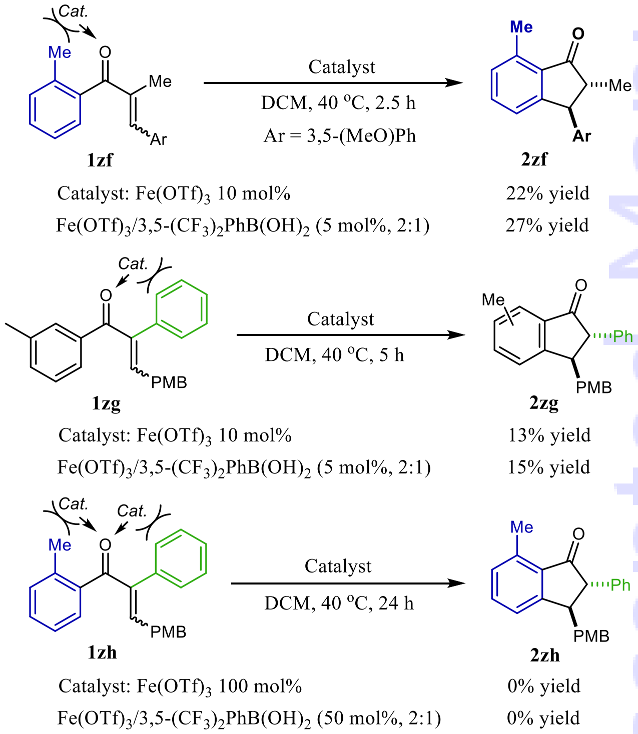
Our catalyst system exhibited a unique activation capacity for the Nazarov reaction,[14f] and realized unprecedented catalytic reactions of electron deficient aryl vinyl ketones and α-unsubstituted chalcones. High resolution mass spectrometer (HRMS) analysis of the catalyst indicated that diiron species were formed in situ.[14g] Attempts to characterize the solution phase complex by a NMR experiment were prevented due to broadening associated with paramagnetic Fe^{3+} species.[14g] However, a preliminary investigation provided pieces of meaningful information at the current stage. The probable TfOH catalysis for the reaction was precluded, since it is catalytically inactive for the challenging electron deficient aryl vinyl ketones and α-unsubstituted chalcones.[14h] The approximate high efficiency of the catalysts $ArB(OH)_2/Fe(OTf)_3$ (1:2) with different aryl boric acids,[14f] combined with the significant effect of the ratio of $3,5\text{-}(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ (Table 1, entry 17 *vs.* 15), is highly suggestive of a diiron catalytic active species for the catalytic Nazarov reaction.

Compared with the unactivated aryl vinyl ketone **1a** (Table 1, entries 7 and 17), the Nazarov reaction of the corresponding polarized aryl vinyl ketone **1ze** proceeded much more efficiently (Scheme 2). The Lewis acid activation and the substrate preactivation played a key role for the Nazarov reaction of polarized aryl vinyl ketones.[3,5,6] In addition, it is more accessible for the activation of aryl vinyl ketones via a chelating approach. Since the diiron species catalyzed unactivated aryl vinyl ketones more efficiently than the $Fe(OTf)_3$ catalyzed polarized aryl vinyl ketones, we thought the diiron species may activate the unactivated aryl vinyl ketones via a simultaneous double coordination approach.



Catalyst	Time	Yield
Catalyst: $Fe(OTf)_3$ 10 mol%	1.5 hours	91% yield
$Fe(OTf)_3/3,5\text{-}(CF_3)_2PhB(OH)_2$ (5 mol%, 2:1)	40 mins	93% yield

Scheme 2. Nazarov reaction of polarized aryl vinyl ketone.



Catalyst	2zf
Catalyst: $Fe(OTf)_3$ 10 mol%	22% yield
$Fe(OTf)_3/3,5\text{-}(CF_3)_2PhB(OH)_2$ (5 mol%, 2:1)	27% yield

Catalyst	2zg
Catalyst: $Fe(OTf)_3$ 10 mol%	13% yield
$Fe(OTf)_3/3,5\text{-}(CF_3)_2PhB(OH)_2$ (5 mol%, 2:1)	15% yield

Catalyst	2zh
Catalyst: $Fe(OTf)_3$ 100 mol%	0% yield
$Fe(OTf)_3/3,5\text{-}(CF_3)_2PhB(OH)_2$ (50 mol%, 2:1)	0% yield

Scheme 3. Control experiments.

To probe the origination of the unique catalytic activity of our catalyst, substrates **1zf-1zh** were subjected to the Nazarov reaction (Scheme 3). The control experiments highlight the significant steric effect and that the *o*-methyl and α-phenyl groups of aryl vinyl ketones prevent the coordination and activation of ketones by catalysts on their sides;[14i] the catalytic efficiency of diiron species is sharply reduced and close to that of $Fe(OTf)_3$ which highly prefers to activate ketones in a single coordination model even in the presence of excess $Fe(OTf)_3$. In principle, the single complexation leaves one sp^2 lone pair free and available for binding a second Lewis acid. In view of this, a bidentate Lewis acid diiron activation via the efficient simultaneous coordination toward carbonyls, which promises to be even more efficient than the single coordination activation mode, was proposed to account for the unique catalytic activity of our catalyst.[10] This was further supported by the IR experiments (Figure 2). The carbonyl region of the spectrum showed a peak at 1641 cm^{-1} corresponding to aryl vinyl ketone **1f** (Figure 2, A). With the treatment of Lewis acids, the carbonyl stretch of the coordinated ketone **1f** showed a large shift (Figure 2, A vs. B and C). The characteristic bands appeared at 1637 cm^{-1} for ketone **1f** bound by $Fe(OTf)_3$ (Figure 2, B), while the carbonyl single disappeared for ketone **1f** coordinated by $(CF_3)_2PhB(OH)_2/Fe(OTf)_3$ (1:2) (Figure 2, C).[14j] The diiron species caused a significantly larger shift to free ketone **1f**, suggesting a more substantial weakening of the carbonyl bond than with $Fe(OTf)_3$.[16] This was a strong signal that the diiron species acted as a bidentate Lewis acid and activated the carbonyls via simultaneous double coordination, which is much stronger than the single coordination of $Fe(OTf)_3$.

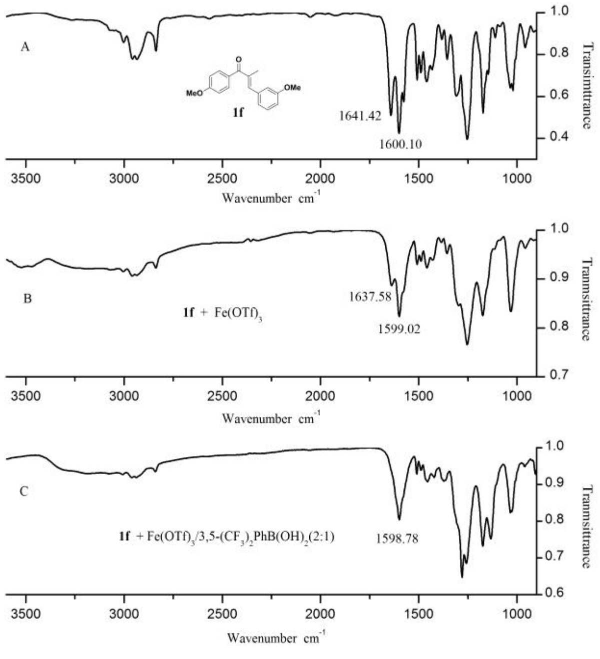
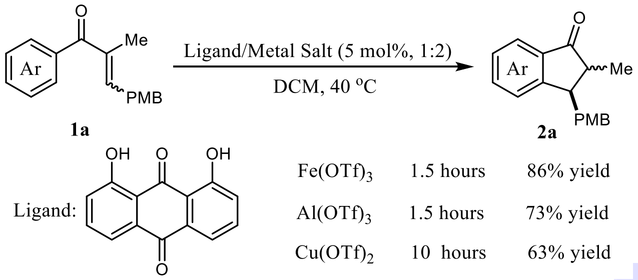


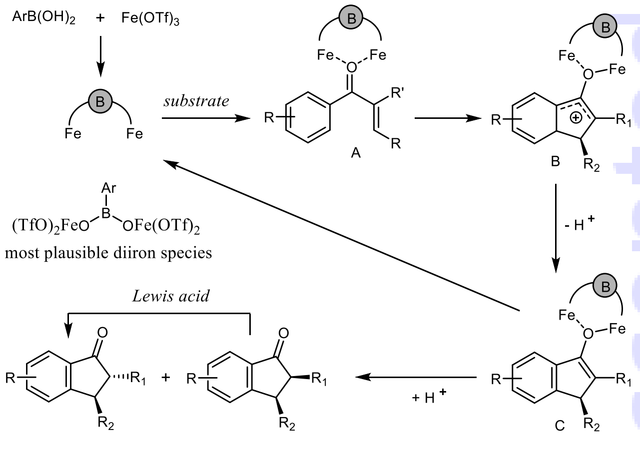
Figure 2. IR analysis for the mechanistic investigation.

The bidentate activation was further strengthened by the application of other bidentate Lewis acids in the Nazarov reactions (Scheme 4). Bidentate Lewis acids could be facilely synthesized via the coordination of binucleating ligands, and have been successfully applied in many reactions.[10,11] Following this strategy, bidentate diiron, bis(aluminium) and dicopper complexes were synthesized,[14f] and demonstrated much higher catalytic efficiencies than the metal salts itself for the Nazarov reaction of aryl vinyl ketones (Scheme 4 vs. Table 1 entries 1, 5 and7).



Scheme 4. Bidentate Lewis acids catalyzed Nazarov reaction of unactivated aryl vinyl ketones.

Based on the control experiments, HRMS analysis, IR analysis and the previous reports,[3] a probable mechanism of the reaction was proposed (Scheme 5). A bidentate Lewis acid diiron species was facilely generated in situ. The catalyst would then double coordinate and activate the aryl vinyl ketones forming a highly active intermediate **A**, which facilely undergoes the 4π-electrocyclizations. The enolate C, formed by the deprotonation of oxoallylic cation **B**, then underwent a kinetic protonation, producing *cis*-favored indanones. Thermodynamically stable *trans*-indanones were finally obtained under the influence of the Lewis acids via reversible enolization of the ketones.[14f]



Scheme 5. Proposed reaction mechanism.

In conclusion, we have developed a catalytic highly efficient Nazarov reaction of unactivated aryl vinyl ketones by using $3,5\text{-}(CF_3)_2PhB(OH)_2/Fe(OTf)_3$. The methodology demonstrated an extremely broad substrate scope, giving the corresponding indanones in high yields as well as high rigioselectivity and diastereoselectivity. Notably, the challenging electron deficient aryl vinyl ketones and α-unsubstituted chalcones have been successfully explored for the first time. Mechanistic investigation supports a bidentate diiron Lewis acid catalysis, and the strong double coordination and activation towards aryl vinyl ketones play key roles for the high catalytic efficiency of the reaction. Further application of the bidentate diiron Lewis acid are currently underway.

Experimental Section

To the solution of 3,5-$(CF_3)_2C_6H_3B(OH)_2$ (0.01mmol, 5 mol%) in 1.0 mL CH_2Cl_2, $Fe(OTf)_3$ (0.02mmol, 10 mol%) was added under nitrogen atmosphere, the resulting mixture was stirred at 40 °C for 30 min. Aryl vinyl ketone (0.2 mmol) was then added, the reaction mixture was stirred at 40°C for indicated time. The product was then directly purified by column chromatography on silica gel.

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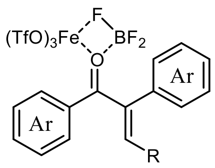

[14] a) Optimization of reaction conditions, for details see the supporting information (SI); b) BF_3 and $Fe(OTf)_3$ were thought to complex via a fluorine atom; c) The *syn* and *anti* determination were made on the basis of coupling constants and NOESY analysis; d) The steric interactions between BF_3/$Fe(OTf)_3$ complexes and the substrate was thought to be much smaller; e) $Cu(OTf)_2$, Fe(III) can not catalyze the reaction, see SI; f) See SI; g) Diiron species were formed in situ by ligand exchange or coordination, see SI; attempts to characterize the catalyst by a NMR experiment or X-ray crystallography were failed; at this stage, diiron species were thought to be responsible for the high reactivity of the Nazarov reaction; h) Reactivity of the reaction was basically maintained with the removal of probable HOTf (bp 168 °C) formed in catalyst preparation using high vacuum pump (0.02mmHg) at 40 °C; i) The steric effect prevented the simultaneous double coordination and activation of carbonyls by the diiron species; j) The disappeared carbonyl single was thought to overlap with the single of conjugated carbon-carbon double bond (Figure 2, C).

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Catalytic Efficient Nazarov Reaction of Unactivated Aryl Vinyl Ketones via a Bidentate Diiron Lewis Acid Activation Strategy

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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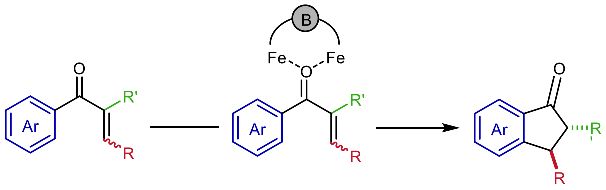

√ bidentate diiron Lewis acid catalysis
√ extremely wide substrate scope

√ mild reaction conditions
√ high yield, high selectivity