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Interrupted Carbonyl-Alkyne Metathesis

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Dedicated to Professor Eric N. Jacobsen on the occasion of his 60th birthday.

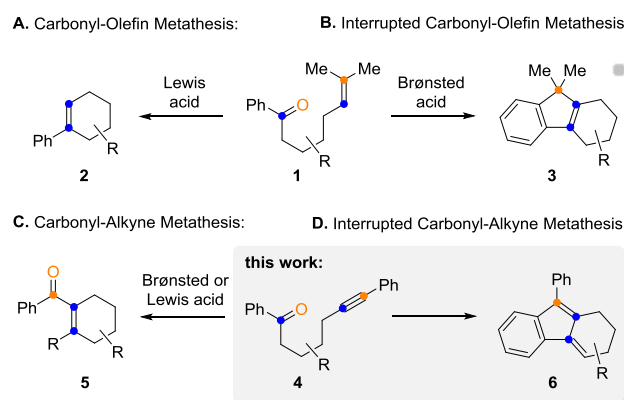
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Abstract. Carbonyl-olefin metathesis and carbonyl-alkyne metathesis represent established reactivity modes between carbonyls, alkenes, and alkynes under Lewis and Brønsted acid catalysis. Recently, an interrupted carbonyl-olefin metathesis reaction has been reported that results in tetrahydrofluorenes via a distinct fragmentation of the reactive intermediate. We herein report the development of an analogous transformation interrupting the carbonyl-alkyne metathesis reaction path resulting in dihydrofluorene products relying on Lewis acidic superelectrophiles as active catalytic species.

Keywords: carbonyl-alkyne metathesis; interrupted carbonyl-alkyne metathesis; superelectrophile; Lewis acid catalysis; Nazarov cyclization

Ring-closing carbonyl-olefin metathesis between carbonyl and olefin functional groups has emerged as a powerful strategy for carbon-carbon bond formation (Fig. 1A).^[1-5] Several Lewis acids have been identified for their ability to catalyze this transformation, including FeCl₃,^[6] GaCl₃,^[7] I₂,^[8] trityl^[9] and tropylium^[10] tetrafluoroborate salts, resulting in a variety of cyclopentenes, cyclohexenes, polyaromatic hydrocarbons, and functionalized pyrrolines. Lewis acid-catalyzed carbonyl-olefin metathesis reactions proceed via an initial [2+2]-cycloaddition to form intermediate oxetanes and a subsequent retro [2+2]-cycloaddition to result in the desired metathesis products.^[11] In comparison, under Brønsted acid catalysis this reaction path was shown to be interrupted to result in the formation of tetrahydrofluorenes **3** (Fig. 1B).^[12] Specifically, a distinct fragmentation of the oxetane via intermediate benzylic carbocations enabled an oxygen-atom-transfer step to ultimately yield the tricyclic products. Additionally, alkyne-carbonyl metathesis relying on Lewis or Brønsted acids has been recognized as an efficient strategy to access substituted enones **5** from carbonyl and alkyne precursors **4** (Fig. 1C).^[13] The



reaction similarly relies on an initial [2+2]-cycloaddition and a subsequent

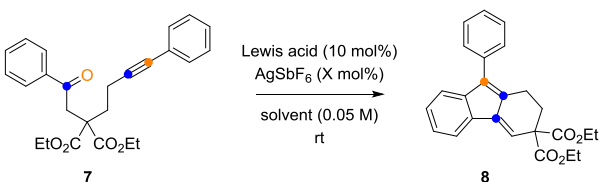
Figure 1. Selected reactivity modes between carbonyls, alkenes, and alkynes under Lewis and Brønsted acid catalysis.

ring-opening transitioning through a strained oxetene intermediate. We herein report that aryl ketones **4** bearing a pendant alkyne can also result in the formation of dihydrofluorenes **6** when converted under catalytic amounts of Lewis acidic superelectrophile^[14] (Fig. 1D). Based on our studies, we propose a reaction path that interrupts carbonyl-alkyne metathesis via a distinct fragmentation of intermediate oxetenes to enable a subsequent Nazarov cyclization resulting in the dihydrofluorene products.

In initial efforts we investigated the conversion of alkyne **7** with catalytic amounts of FeCl₃ and observed the formation of dihydrofluorene **8** as a new product in 40% yield, albeit with near complete conversion of the starting material (entry 1, Table 1). Subsequent attempts focused on the evaluation of additional, simple Lewis acids, however the results obtained proved inferior and did not produce significant amounts of dihydrofluorene **8**. We have recently shown that Lewis acidic superelectrophiles can function as potent catalysts for the activation of

less reactive substrates in carbonyl-olefin metathesis reactions.^[15] Specifically, suitable silver salts can abstract halides X from neutral metal complexes MX_n

Table 1. Reaction optimization relying on Lewis acid



entry	Lewis acid	AgSbF ₆ (X mol%)	solvent	yield 8 (%)	conv. (%)
1	FeCl ₃	-	DCE ^a	40	98
2	AlCl ₃	10	DCE	61	90
3	FeCl ₃	10	DCE	37	69
4	InCl ₃	10	DCE	50	93
5	GaCl ₃	10	DCE	62	100
6	ZnCl ₂	10	DCE	0	5
7	AlCl ₃	20	DCE	25	55
8	GaCl ₃	20	DCE	70	96
9	GaCl ₃	30	DCE	42	99
10	GaCl ₃	20	DCM	74	100
11	GaCl ₃	20	benzene	55	70
12	GaCl ₃	20	toluene	61	100
13	GaCl ₃	20	PhCl	91	99
14	GaCl ₃	20	PhCF ₃	98	99
15	-	20	PhCF ₃	7	42
16	GaCl ₃	-	PhCF ₃	64	88
17	-	SbF ₅ (10 mol%)	PhCF ₃	62	100

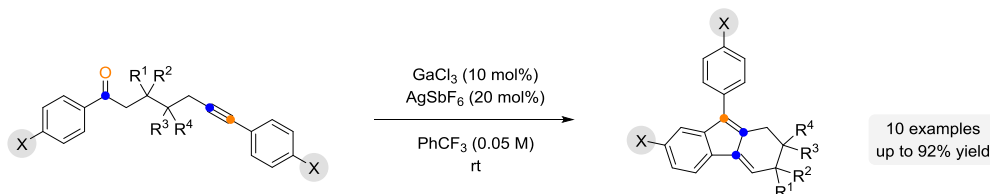
Conditions: All reactions were performed using 0.10 mmol of the substrate at room temperature for 14-24 h. Yields and conversions are reported as ¹H-NMR yields with phenyltrimethylsilane as an internal standard. ^a reaction conducted at 80°C.

superelectrophiles.

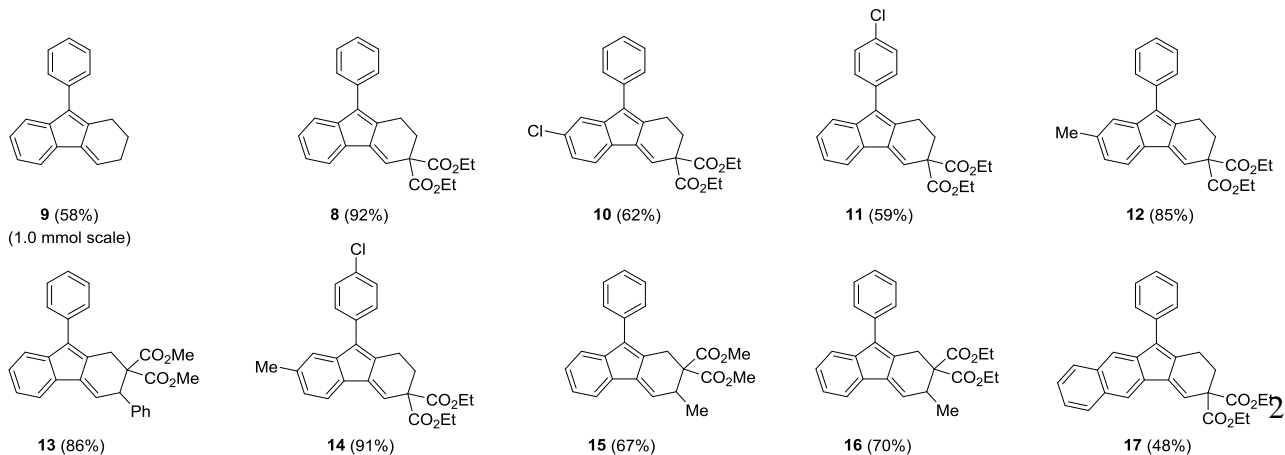
resulting in the formation of superelectrophilic heterobimetallic ion pairs.^[16] Based on these results, we next evaluated various Lewis acid superelectrophiles, obtained via chloride abstraction from neutral Lewis acids, for their ability to catalyze the formation of **8**. Specifically, the ion pair [AlCl₂]⁺[SbF₆]⁻ generated from equimolar amounts of AlCl₃ and

Table 2. Substrate Scope.

AgSbF₆ provided dihydrofluorene **8** in an increased yield of 61% (entry 2, Table 1). Subsequent investigations focused on evaluating Lewis acids varying in strength, including FeCl₃, InCl₃, GaCl₃, and ZnCl₂, in combination with AgSbF₆ as the silver salt (entries 3-6, Table 1). The corresponding heterobimetallic ion pairs provided the desired dihydrofluorene **8** in up to 62% yield. Importantly, [GaCl₂]⁺[SbF₆]⁻ resulting upon chloride abstraction from GaCl₃ was identified as the most promising catalyst (entry 5, Table 1). Subsequent efforts focused on varying the ratio of neutral metal salt, AgSbF₆ (entries 7-9, Table 1). When heterobimetallic ion pair [AlCl₂]⁺ 2[SbF₆]⁻ was generated upon chloride abstraction from AlCl₃ with two equivalents of AgSbF₆, diminished yields of **8** were observed in 25% (entry 7, Table 1). Nevertheless, [GaCl₂]⁺ 2[SbF₆]⁻ generated *in situ* proved superior and resulted in the desired product in 70% yield (entry 8, Table 1). Conversely, increased loadings of AgSbF₆ (30 mol%) together with 10 mol% GaCl₃ were shown to be inferior resulting in diminished yields of 42%. Subsequently, we focused on the evaluation of additional solvents and identified that electron-deficient aromatic solvents resulted in increased yields of dihydrofluorene **8** (entries 10-14, Table 1). Ultimately, 10 mol% GaCl₃ and 20 mol% AgSbF₆ in 0.05 M trifluorotoluene at room temperature were established as optimal, resulting in the formation of dihydrofluorene **8** in 98% yield (entry 14, Table 1). Importantly, converting aryl ketone **7** with either 20 mol% AgSbF₆ or 10 mol% GaCl₃ resulted in diminished yields of **8** in 7% and 64%, respectively, suggesting that both metal salts are required to form the optimal catalyst (entries 15 and 16, Table 1). We also considered the possibility that this heterobimetallic ion pair could fragment *in situ* to result in the formation of SbF₅ as a strong Lewis acid catalyst. However, when aryl ketone **7** was converted with catalytic amounts of SbF₅ under otherwise optimal reaction conditions, the desired product was



Substrate Scope:



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Conditions: All reactions were performed using 1.0 equivalents of the substrate, GaCl₃ (10 mol%), and AgSbF₆ (20 mol%) in PhCF₃ (0.05 M) at room temperatures for 18-24h.

generated in diminished yields of 62% (entry 17, Table 1).

The optimal reaction conditions identified proved general for a variety of electronically and sterically differentiated dihydrofluorenes (Table 2). Specifically, the unsubstituted dihydrofluorene **9** was generated in 58% yield while bisester **8** was formed in 92% yield, respectively, demonstrating that a Thorpe-Ingold effect is beneficial for the transformation. Both electron-rich and -poor aryl ketones were tolerated under the optimized reaction conditions, providing chloro-substituted product **10** in 62% overall yield and methyl-substituted product **12** in 85% yield. Electron-deficient substituents on the alkyne moiety were tolerated and *para*-chlorinated dihydrofluorenes **11** and **14** were obtained in 59% and 91% yield, respectively. Additionally, substitution on the carbon backbone incorporating large aromatic moieties or smaller aliphatic substituents was well tolerated resulting in the formation of the desired dihydro-fluorene products in up to 86% yield (**13**, **15**, **16**, Table 2).

The formation of dihydrofluorene **21** has been reported by Miura and coworkers upon treatment of aryl ketone **18** with catalytic amounts of $\text{In}(\text{OTf})_3$ in

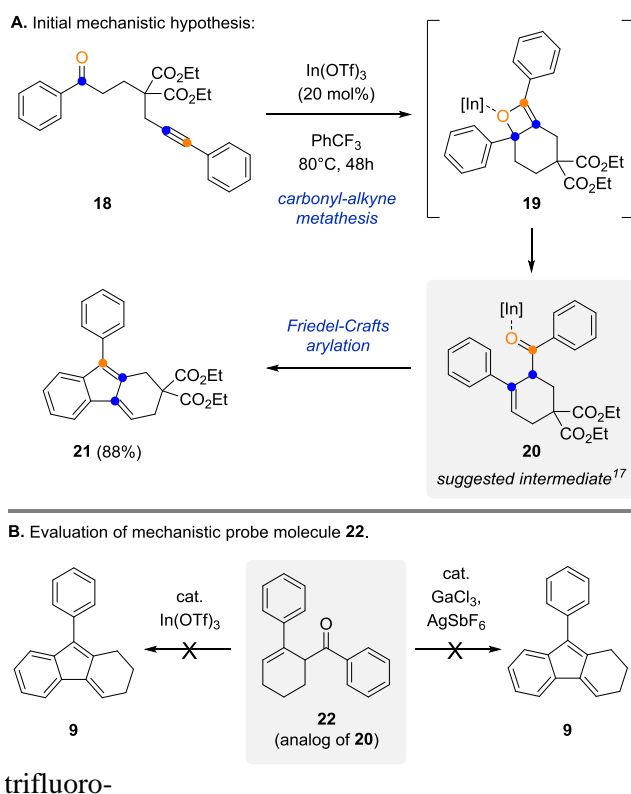
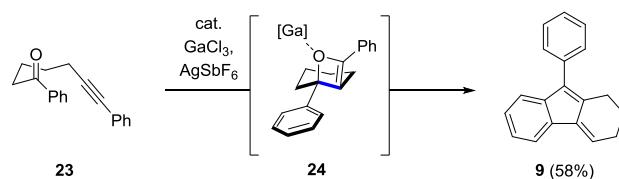


Figure 2. **A.** Proposed initial mechanistic hypothesis relying on carbonyl-alkyne metathesis and Friedel-Crafts arylation. **B.** Mechanistic probe **22** converted under optimal conditions.

A. Conversion of aryl ketone **23 to fluorene **9**.**



B. Revised mechanistic hypothesis.

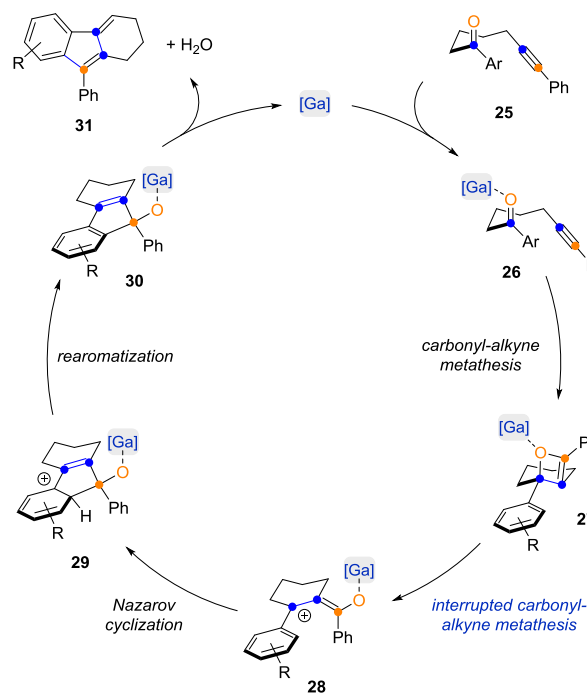


Figure 3. **A.** Conversion of aryl ketone **23** to dihydrofluorene **9** in 58% yield. **B.** Revised mechanistic hypothesis for the formation of dihydrofluorenes **31** via interrupted carbonyl-alkyne metathesis.

toluene at elevated temperatures (Fig. 2A).^[17] The authors suggest a reaction path that relies on initial metal enolate formation and subsequent addition into the activated alkyne to result in the formation of an intermediate vinylic carbocation. This carbocation is trapped by the metal enolate to form cyclohexene **20** that upon final Friedel-Crafts arylation gives rise to dihydrofluorene **21**. We hypothesized that an alternate mechanistic scenario could rely on an initial carbonyl-alkyne metathesis via oxetene **19** that upon cycloreversion either results in the tetrasubstituted alkene or its isomerized cyclohexene analog **20** (Fig. 2A). To investigate these mechanistic hypotheses, we synthesized mechanistic probe molecule **22** as an analog of the proposed intermediate **20** (Fig. 2B). However, when **22** was converted under our optimal reaction conditions relying on catalytic GaCl_3 and AgSbF_6 or the conditions reported by Miura utilizing catalytic amounts of $\text{In}(\text{OTf})_3$, the desired product **9** was not observed. Nevertheless, aryl ketone **23** was shown to be a viable substrate under our optimal reaction conditions resulting in the formation of dihydrofluorene **9** in 58% yield (Fig. 3A). Based on

these results, we considered an alternate reaction path that relies on distinct oxetene fragmentation and is inspired by our previous insights obtained in interrupted carbonyl-olefin metathesis reactions (Fig. 3B). Specifically, we propose an initial activation of aryl ketone **25** with the Lewis acid superelectrophile to result in Lewis acid-base complex **26**. This complex subsequently undergoes carbonyl-alkyne metathesis to form oxetene **27** as a reactive intermediate. Rather than undergoing a cycloreversion following established carbonyl-alkyne metathesis, we hypothesize that oxetene **27** can fragment to result in the formation of a benzylic carbocation **28**. This divergent fragmentation interrupts the carbonyl-alkyne metathesis reaction path to result in **28** as a distinct intermediate that can undergo a subsequent Nazarov cyclization to yield the tricyclic carbon core. Rearomatization of **29** results in cyclohexene **30** which upon elimination of water results in dihydrofluorene **31** and the regeneration of the Lewis acid catalyst.

We describe the development of a Lewis acid-catalyzed transformation between carbonyl and alkyne functional groups to result in the formation of functionalized dihydrofluorene products. The reaction relies on Lewis acidic superelectrophiles as active catalytic species and proved general for a variety of substituted aryl ketones bearing pendant alkyne moieties. We propose a reaction path that interrupts established carbonyl-alkyne metathesis reactions via a distinct fragmentation of intermediate oxetenes to result in benzylic carbocations. A subsequent Nazarov cyclization and rearomatization results in the tricyclic carbon core structure and ultimately yields the desired dihydrofluorene products.

Experimental Section

A flame-dried flask was charged with **7** (0.17 mmol), GaCl₃ (0.017 mmol), AgSbF₆ (0.034 mmol), and trifluorotoluene (0.05 M) under a nitrogen atmosphere. The resulting mixture was allowed to react at room temperature for 24 hours. The reaction was subsequently filtered through a plug of silica eluting with DCM. The filtrate was concentrated under reduced pressure to remove all volatile components. The crude material was purified using column chromatography to afford **61** mg (92% yield) of **8**.

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