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Friedel–Crafts acylation *via* interrupted Beckmann fragmentation of activated ketones

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Friedel–Crafts (FC) acylation has long been a fundamental electrophilic arene substitution reaction. In this work, we report a new procedure for FC acylation utilizing stable and user-friendly acylium precursors, α -oximinoketones. The key to this methodology is the selective C_{sp^2} – C_{sp^2} bond cleavage in α -oximinoketones, facilitated by triflic anhydride, leading to the formation of acylium ions under mild conditions. This approach demonstrates compatibility with a variety of substituted alkyl, (hetero)aryl ketones, and cyclic ketones as acylating reagents, where cyclic ketones allow for unique ring-opening FC acylation without relying on ring strain. DFT calculations confirmed the mechanistic pathway, highlighting the generation of acylium ions *via* the selective Beckmann fragmentation over Beckmann rearrangement.

Introduction

Friedel–Crafts (FC) acylation is a well-established electrophilic aromatic substitution reaction that facilitates the formation of aryl ketones. Conventional approaches to this transformation involve generating acylium ions, typically produced by activating carboxylic acids, acyl chlorides, or anhydrides under the strong Brønsted or Lewis acids (Scheme 1A).¹ Owing to its high efficiency, regioselectivity, and controlled monoacylation, FC acylation has been widely utilized for the construction of various aryl ketones. Furthermore, it serves as a critical step in the stepwise synthesis of alkyl arenes following the reduction of the ketone group.² However, one significant limitation of traditional methods is that the acylation reagents such as acyl chlorides and anhydrides are often hazardous or unstable due to moisture-sensitivity. Additionally, the industrial synthesis of acyl chlorides remains largely reliant on toxic and corrosive thionyl chloride.

Although less commonly used, alternative carboxylic acid derivatives have been sporadically reported for use in FC acylation (Scheme 1B). However, their reduced reactivity compared to that of acyl chlorides often necessitates elaborate structural modifications and/or harsh reaction conditions at elevated temperatures. For example, C–O bond activation of *t*-butyl ester, activated esters, and directing group-containing esters was enabled by catalytic $InBr_3$ and dimethylchlorosilane,³ $TfOH$,⁴ and $AlCl_3$,⁵ respectively. Nonactivated methyl benzoate required elevated temperature in the presence of 5 equiv. $TfOH$, with the proposal of highly reactive dicationic intermediates.⁶ Simple benzyl esters were also utilized as acylating reagents through

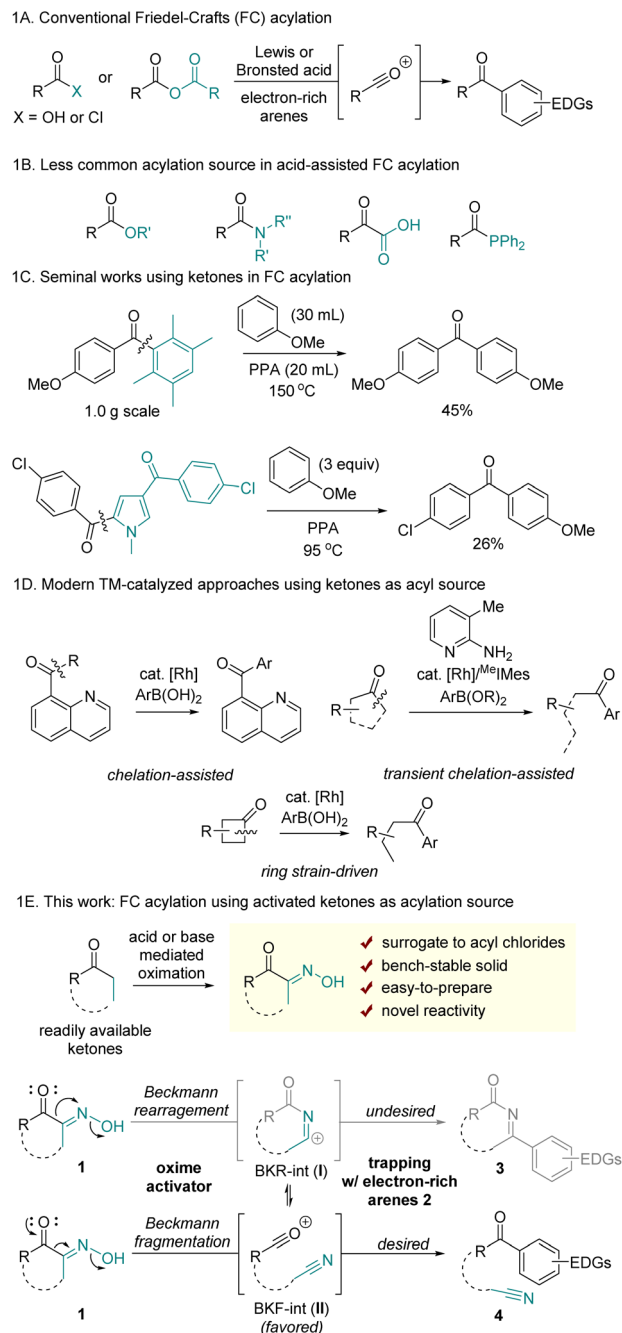
acyl chloride intermediates when reacted at 130 °C with PCl_3 and I_2 .⁷ Amides, that possess a more robust C–N bond, have also been reported as viable sources for FC acylation. For instance, β -lactam has been employed in FC acylation *via* strain-driven ring-opening acylation.⁸ Electronically tuned⁹ or sterically distorted amides¹⁰ have demonstrated utility as acyl sources, with the weakening of the amide resonance structure proposed to enable C–N cleavage. Despite the limited scope and low efficiency, α -ketoacids have been studied as acylation sources involving decarbonylation pathways.¹¹ More recently, acylphosphine was reported as a suitable source in FC acylation. The C–P bond activation was enabled with $MeOTf$, affording highly electrophilic acylphosphonium salts.¹²

The use of ketones in FC acylation is uncommon owing to the absence of a suitable leaving group. In 1885, Louise demonstrated acid-promoted hydrolytic C(mesityl)–C(carbonyl) cleavage of mesityl phenyl ketone, driven by steric distortion and concomitant frustrated conjugation.¹³ A seminal work applying this reactivity in FC acylation was reported by Vittimberga; it describes a transacylation reaction involving C–C bond cleavage of duryl anisidyl ketone with anisole under harsh conditions. This reaction led to symmetrical dianisidyl ketone, with durene acting as leaving group (Scheme 1C).¹⁴ Later, Keumi demonstrated that pentamethylbenzene also serves as an efficient leaving group.¹⁵ However, this intriguing transacylation method has had limited practical application for decades, probably due to its limited scope. The Donohoe group recently utilized acid-mediated C(pentamethylphenyl)–C(carbonyl) cleavage for the post-functionalization of α,α -di-alkylpentamethylphenylketones.¹⁶ The related early example was also found in Carson's study using acylpyrrole; the electron-rich pyrrole was identified as a leaving group in acidic conditions, albeit displaying low efficiency.¹⁷ Despite limited

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Scheme 1 Prior art in Friedel-Crafts acylation and reaction design using ketones.

examples and practical challenges of using ketones in FC acylation, employing ketones or their synthetic analogs offers significant advantages in reaction scope, as ketones are prevalent in many organic molecules and readily available.

Apart from the conventional acid-assisted acylation of arenes, modern approaches have been developed *via* transition metal-catalysis, photocatalysis, and electrocatalysis to afford unsymmetrical aryl ketones. While these novel synthetic methods have been enabled with various carbonyl sources through C(carbonyl)-X bond activations (X = halogens, O, N, S,

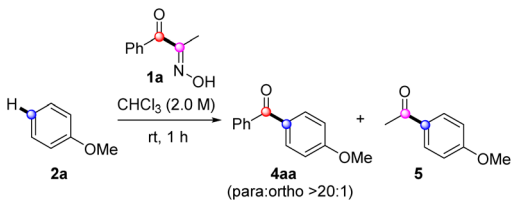
H, Si, *etc.*),¹⁸ synthetic protocols using ketones as acylation reagents remain limited. Recently, acylation of arenes using ketones was reported through chelation-assisted¹⁹ or ring strain-driven C-C bond activation,²⁰ followed by Suzuki-Miyaura type cross-coupling reactions between C-TM-C intermediates and aryl boronic acid derivatives (Scheme 1D).

Herein, we present a new method for FC acylation using activated ketones **1** (Scheme 1E). This method features the use of bench-stable precursors to generate acylium ions while maintaining reactivity comparable to that of acyl chlorides. Additionally, by employing ketones as acylation sources, this method enables distinct ring-opening FC acylation using cyclic ketones, without relying on strained ring systems. Previously reported ring-opening FC acylation, not relying on ring-strain, primarily focused on the use of cyclic anhydrides.²¹ A key principle of our reaction design is based on Beckmann fragmentation (BKF), a process that competes with the Beckmann rearrangement (BKR) of oximes. We hypothesized that key acylium ions **II** could be generated *via* the BKF of α -oximino-ketones **1**, and **II** would subsequently be trapped by electron-rich arenes to afford aryl ketones **4**. Since intermediates **I** and **II** can exist in equilibrium following BKR and BKF, the formation of **II** should be thermodynamically and/or kinetically favored over **I** to achieve the desired transformation. Therefore, it is crucial to identify reaction conditions that increase population of **II** without interference with the nucleophilic addition of arenes. While previous studies have demonstrated selective C-C fragmentation of α -carbonyl oximes followed by trapping with nucleophiles such as hydroxide,²² alkoxides,²³ thiolates,²⁴ chloride,²⁵ amines,²⁶ and fluorides,²⁷ a tailored oxime-activation condition is required to achieve C-C fragmentation that is devoid of competitive nucleophilic components other than arenes. Importantly, the activator itself or the byproducts formed during generation of **II** should not react with either the electron rich arenes or **II**.

Results and discussion

The optimization process commenced with identifying a suitable activation system. Strong Brønsted acids, such as methanesulfonic or trifluoromethanesulfonic acids, were initially examined (entries 1 and 2), but no conversion of **1a** was observed. $\text{BF}_3\text{-OEt}_2$ (entry 3) did not afford **4aa** despite full conversion of **1a**. The use of aluminum chloride and perfluorophenylboronic acid showed minimal conversion of **1a**, without forming **4aa** (entries 4 and 5). The dehydroxylative coupling reagent, DCC, also proved ineffective as activator (entry 6). When we shifted our focus to the highly electrophilic triflic anhydride (entry 7), it afforded **4aa** in 64% yield. Increasing the amount of triflic anhydride slightly increased yield of **4aa** (entry 8). Gratifyingly, using 1.5 equivalents of **1a** significantly improved the yield of **4aa** (entries 9 and 10). In this case, a minor byproduct, acetylated arene **5** was obtained, probably arising from hydrolysis of **3aa** or from acylation of **2a** with acetonitrile. However, using **2a** in excess did not affect the yield (entry 11). An attempt at FC acylation under the near neutral pH-conditions with triethylamine was unsuccessful



Table 1 Reaction optimization^a


Entry	Conditions	1a (equiv.)	2a (equiv.)	Yield ^b (%)
1	MsOH (1.2 equiv.)	1	1	No conv.
2	TfOH (1.2 equiv.)	1	1	No conv.
3	BF ₃ -OEt ₂ (1.2 equiv.)	1	1	4aa (0), 5 (0)
4	AlCl ₃ (1.2 equiv.)	1	1	Low conv.
5	F ₅ -PhB(OH) ₂ (10 mol%)	1	1	Low conv.
6	DCC (1.2 equiv.)	1	1	4aa (0), 5 (0)
7	Tf ₂ O (1.2 equiv.)	1	1	4aa (64), 5 (0)
8	Tf ₂ O (1.5 equiv.)	1	1	4aa (71), 5 (0)
9	Tf ₂ O (2.25 equiv.)	1.5	1	4aa (91), 5 (2)
10	Tf ₂ O (3 equiv.)	2	1	4aa (90), 5 (3)
11	Tf ₂ O (1.2 equiv.)	1	2.5	4aa (76), 5 (7)
12	Tf ₂ O (1.2 equiv.), Et ₃ N (2.4 equiv.)	1	2.5	No conv.
13	DCM instead of CHCl ₃	1.5	1	4aa (77), 5 (2)
14	THF, DMF, or DMSO instead of CHCl ₃	1.5	1	4aa (0), 5 (0)
15	EtOAc instead of CHCl ₃	1.5	1	4aa (27), 5 (0)
16	CH ₃ CN instead of CHCl ₃	1.5	1	4aa (14), 5 (0)
17	1.0 M instead of 2.0 M	1.5	1	4aa (76), 5 (0)
18	3.0 M instead of 2.0 M	1.5	1	4aa (64), 5 (0)
19	0 °C instead of rt	1.5	1	4aa (26), 5 (0)

^a Reaction condition: **2a** (0.3 mmol), **1a** (0.45 mmol), Tf₂O (0.68 mmol) and CHCl₃ (0.23 mL), rt, 1 h. ^b Isolated yield.

(entry 12). The solvent effect was significant. A chlorinated solvent such as DCM was only comparable solvent among tested. More polar solvents including THF, DMSO, DMF, EtOAc, and CH₃CN yielded complicated mixture or exhibited low conversion (entries 13–16). When examining concentration dependence, neither lower (1.0 M) nor higher concentration (3.0 M) were comparable to 2.0 M (entries 17 and 18). In addition, the reaction was sluggish at 0 °C, resulting in low conversion (entry 19) (Table 1).

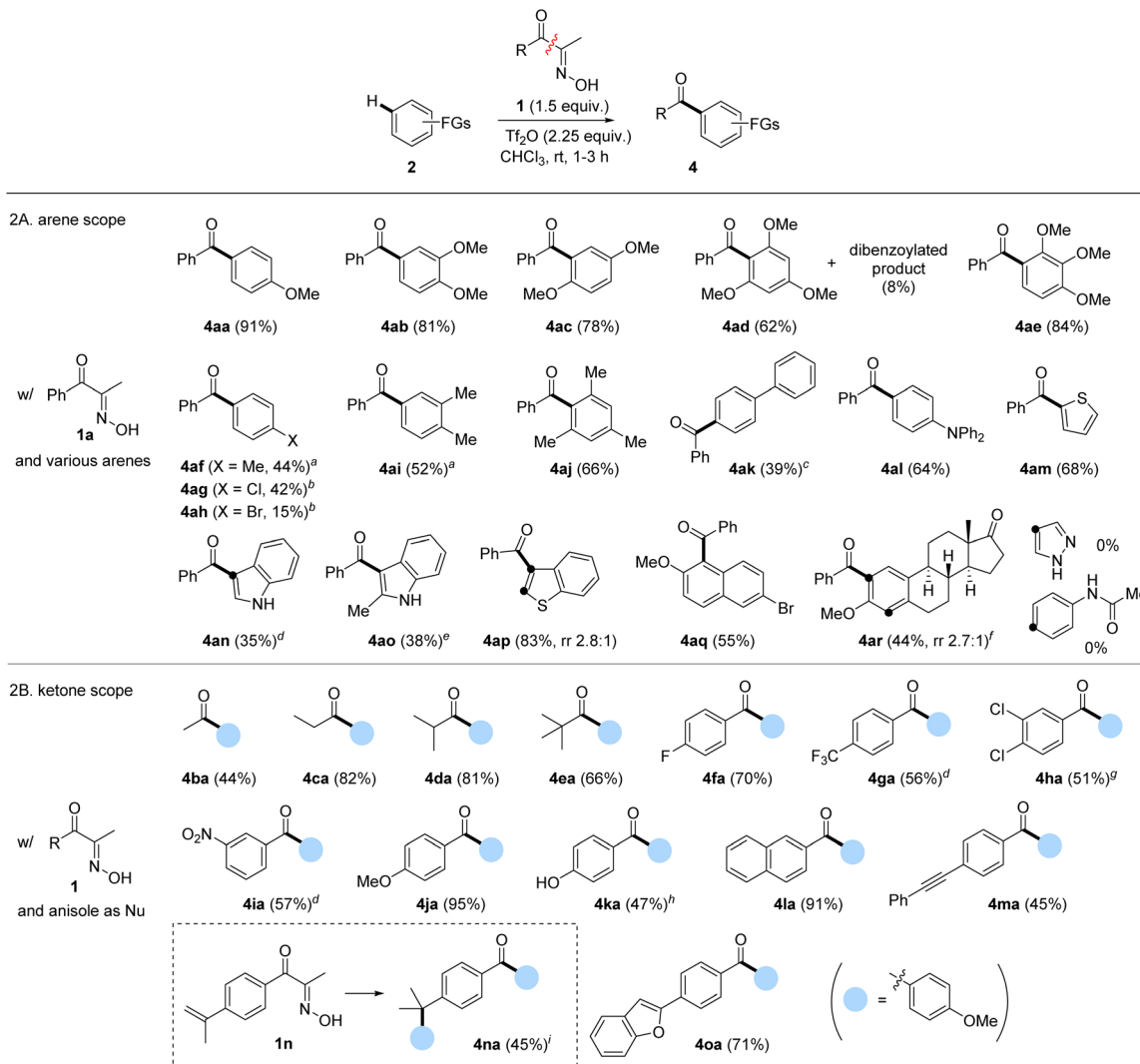
With the optimal conditions established, we explored the arene scope using **1a** as the acylation source (Scheme 2A). Some isomeric dimethoxybenzenes and trimethoxybenzenes underwent FC acylation smoothly, exhibiting excellent regioselectivities (**4ab–4ac**). However, near-electron-neutral toluene showed decreased yield of **4af**; the yield was slightly improved under elevated temperature. The electronically deactivated halobenzenes showed extremely low reactivity, which improved when using dichloroethane (DCE) as solvent at 100 °C (**4ag–4ah**). As expected, introducing additional methyl groups on the arene, which enhanced electron density, positively influenced FC acylation (**4ai** and **4aj**). Biphenyl **2k** showed similar reactivity and resulted in a yield comparable to that of toluene. Electron-rich triphenylamine was also a suitable nucleophile, affording

4al in a 64% yield. Other electron-rich (hetero)arenes, such as indoles, thiophene, benzothiophene, and naphthalene, delivered the corresponding benzoylated products **4am–4aq** in moderate to good yields. Finally, we evaluated a biomolecule such as estrone derivative **2r**, which afforded acylation products **4ar** with a ratio of 2.7 : 1.²⁸ Overall, the tested electron-rich arenes under the developed protocol with **1a** resulted in moderate to excellent isolated yields of acylation. However, pyrazole and acetanilide were unsuitable nucleophiles for FC acylation under these conditions, while pyrazole underwent *N*-benzoylation as a major side reaction.

Next, we investigated the scope of α -oximinoketones as acylation sources (Scheme 2B).²⁹ The acylation with alkyl ketones was effective under the optimized conditions, enabling acetylation (**4ba**), propanoylation (**4ca**), isobutanoylation (**4da**), and pivaloylation (**4ea**) of anisole with moderate to excellent yields (44–82%).³⁰ The effects of substituents on aryl ketones were then tested. Arenes bearing electron-withdrawing groups (**4fa–4ia**) were compatible, resulting in moderate to good yields (51–70%). Among those, **4ga–4ia** required elevated temperatures. An electron-rich *p*-methoxyphenyl ketone afforded a symmetrical dianisidyl ketone **4ja** in excellent yield (95%), likely due to the stabilization of the acylium ion by the *p*-methoxy group. Notably, the potentially competing phenol **1k** gave the desired product **4ka** when excess anisole was employed. Additionally, naphthyl ketone produced the corresponding biaryl ketone **4la** in a 91% yield. Acid-sensitive unsaturated bonds were subsequently investigated. While internal alkyne was tolerated (**4ma**), the α -methylstyryl group reacted with anisole to produce the diarylated compound **4na** in a 45% yield. Finally, biaryl ketone containing a latent nucleophile, such as benzofuran, was tested, which afforded the desired product **4oa** in a 71% yield.

Compared to carboxylic acid derivatives, our strategy enables the use of cyclic acylation sources for distinctive ring-opening FC acylation (Scheme 3). During studies on the ring-opening FC acylation, chloroform was observed to be much less efficient for cyclic oximinoketones. After an extensive survey, we identified the TFA-DCM co-solvent or 1,2-dichloroethane (DCE) as the optimal solvent system, which were applied in the reaction scope.³¹ For benzofused cyclic ketones, 6-membered α -oximinoketones derived from 1-tetralones and chromanone underwent ring-opening FC acylations, giving diarylketones **7a–7d** in moderate yields (62–38%). The ring size appears to have a greater influence on the conversion. For instance, 7-membered ketone **6e**, derived from benzosuberone, gave the desired product **7e** with the improved yield (70%) compared to 1-tetralones. Note that using *p*-anisoyl chloride as an acylation source with *o*-cyanoalkylarenes could serve as a reverse disconnection approach to prepare *o*-cyanoalkyl diarylketones **7a–7d**. However, achieving *ortho*-selectivity while overcoming steric hindrance is very challenging. Oximes derived from 2-tetralones were also found to be suitable substrates in ring-opening FC acylation, affording alkyl aryl ketones **7f–7h** in moderate yields. While aryl acylium ions have been known to be more stable than alkyl acylium ions,³² the conversion of these different types acylium ions generated from tetralone series into the corresponding





Scheme 2 Reaction scope. Reaction condition: **2** (0.3 mmol), **1** (0.45 mmol), Tf₂O (0.68 mmol), CHCl₃ (0.23 mL), rt, 1 h. ^a80 °C, ^b100 °C in DCE for 12 h, ^c80 °C for 16 h, ^d60 °C, ^e2o (0.3 mmol) and **1a** (0.3 mmol) at 60 °C, ^frun with Tf₂O (0.45 mmol), ^g40 °C in 0.5 M, ^hrun with **2a** (3 mmol) and **1k** (0.3 mmol), 60 °C, ⁱ**2a** (0.45 mmol), ^j**1n** (0.3 mmol), and Tf₂O (0.45 mmol).

products were comparable. 9,10-Phenanthrene monoxime also proved suitable, affording structurally intriguing product **7i** in 53% yield. Non-benzofused cyclic ketones were subsequently examined. A sterically hindered acylium ion precursor, 5-membered ketone **6j**, resulted in a significantly reduced yield (26%). Non-fused simple 6-membered cyclic ketones yielded the corresponding ring-opening FC acylation products **7k** and **7l** with relatively low efficacy, but synthetically useful yields (28% and 39%). Increasing the ring size to 8 or 12 improved the yields, affording products **7m** and **7n** in 43% and 64% yields, respectively. Interestingly, when conjugated ketone **6o** was tested, the FC acylation was followed by intramolecular alkylation, giving highly substituted indanone **7o** in 40%. However, some oximes derived from 1-indanone (**6p**), dimedone (**6q**), isophorone (**6r**), nootkatone (**6s**), and (+)-4-cholesten-3-one (**6t**) did not give the desired acylation product despite full conversion of the starting materials. While the exact reason is unclear, the enone containing an exo-olefin, *e.g.* pulegone, showed compatibility under the

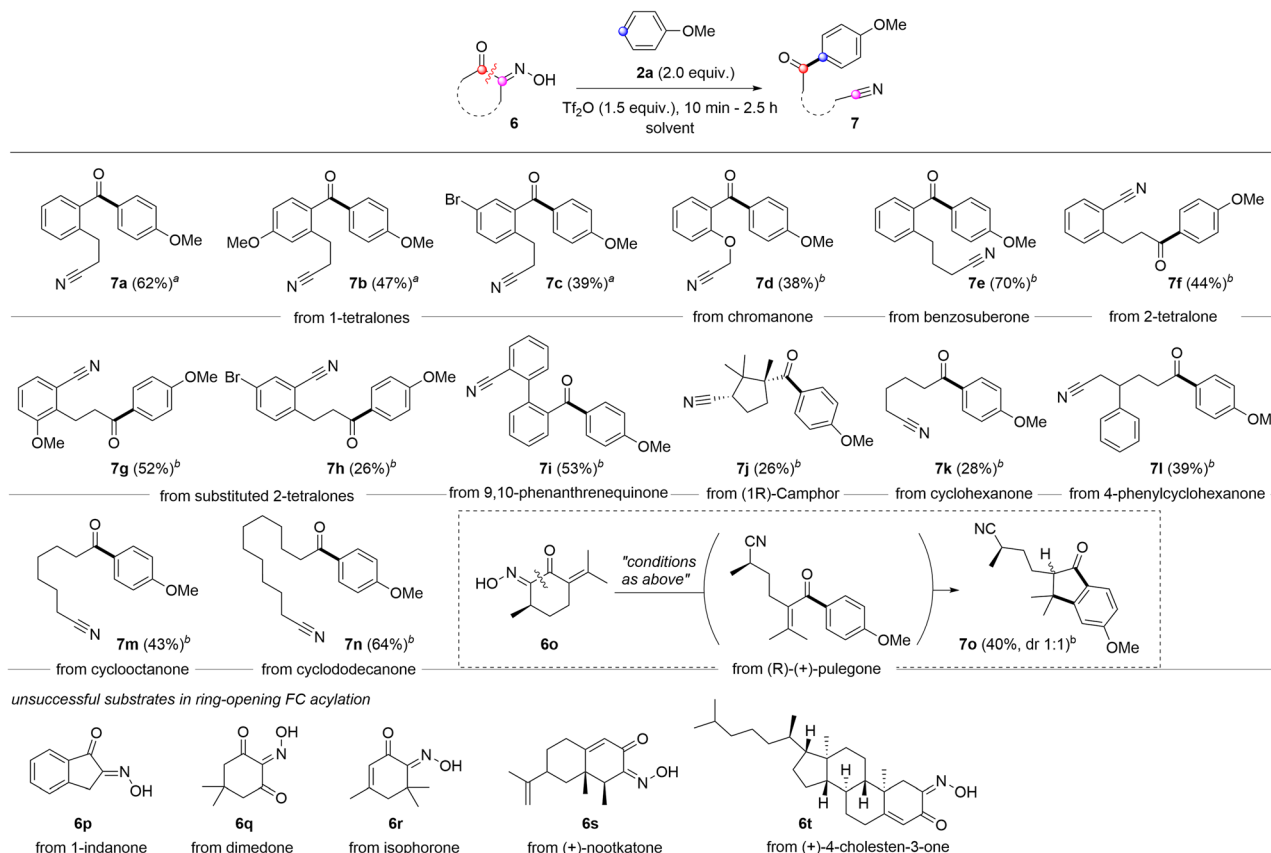
given conditions, whereas those containing endo-olefins, *e.g.* isophorone, nootkatone, and (+)-4-cholesten-3-one, did not.

To further demonstrate the practicality of this method, a gram-scale reaction using **1a** was carried out (Scheme 4A). Ketone and nitrile functionalities are potentially good handles for further derivatization (Scheme 4B). Some simple functional group transformations were exemplified using **7f** as starting material. For instance, selective hydrolysis of the nitrile gave primary amide **8**. Ketone-directed sp² C–H alkenylation afforded compound **9**.³³ Lastly, ketone reduction followed by intramolecular FC alkylation was attempted, leading to 4-cyano-9-arylfluorene **10** with a 65% yield over two steps.

Reaction mechanism

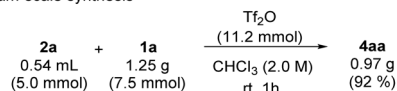
While S_N1-like elimination–addition process in general FC acylation is likely the main elementary steps of the pathway of our FC acylation protocol, we were provoked by the two possible



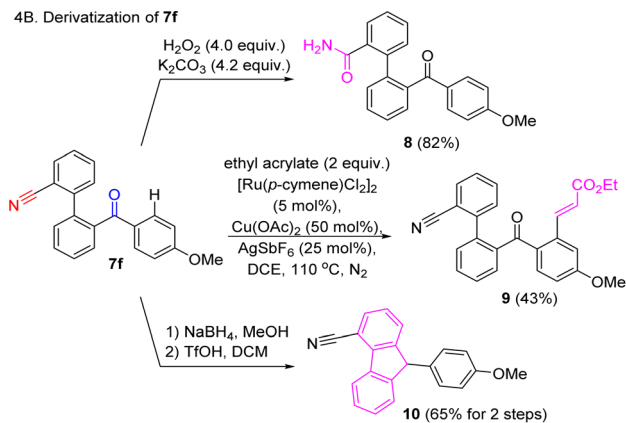


Scheme 3 Reaction scope for ring opening FC acylation. Reaction condition: **6** (0.3 mmol), **2a** (0.6 mmol), Tf₂O (0.45 mmol), rt, 1 h. ^arun in TFA-DCM (8 : 2) (2 M, 0.15 mL), ^brun in DCE (2 M, 0.15 mL).

4A. Gram-scale synthesis



4B. Derivatization of **7f**



Scheme 4 Further transformation.

competing routes for the generation of acylium ions from α -oximinoketones **1**. Observing the excellent selectivity toward BKF and previous reports about the selective C–C cleavage of **1**, we sought to gain more insight into the selectivity between BKR and BKF in terms of energy differences. Looking in the

literature, there was no previous computational studies for the two competing pathways, BKR and BKF, derived from α -oximinoketones. Here, we detailed the relevant DFT studies.

DFT calculations were carried out with focuses on energy profiles when **IN1** diverges *via* the BKR and BKF processes (Fig. 1).³⁴ We investigated the reaction mechanism and Gibbs energy profile using oxime **1a** and Tf₂O as model substrates. In the proposed pathway, defined here as Path-1, the reaction initiates with the activation of oxime **1a** by Tf₂O, leading to intermediate **IN1** *via* **TS1**. This step proceeds with a significant energy barrier of 31.2 kcal mol⁻¹.³⁵ In **TS1**, key bond changes include O–S bond formation (1.80 Å) between the oxime and Tf₂O, accompanied by S–O bond cleavage (2.05 Å) of Tf₂O, a new O–H bond formation (1.05 Å), and the cleavage of the oxime's original O–H bond (1.65 Å). The release of TfOH leads to the formation of **IN1**, which is at +4.4 kcal mol⁻¹. **IN1** subsequently undergoes bond fragmentations through **TS2** (9.5 kcal mol⁻¹), involving C–C bond cleavage (2.55 Å) and N–O bond dissociation (2.07 Å), to generate the stabilized acylium ion intermediate **IN2**, paired with TfO⁻, at 8.6 kcal mol⁻¹.³⁶

As the competing process, we next calculated the energy states of the BKR intermediates. Migration of the acyl group to the nitrogen atom of oxime can lead to the BKR intermediate **IN2-a**, which can have a resonance form **IN2-b**. Acylium ion **IN2-c** coordinated with CH₃CN, derived from **IN2-a** or **IN-b** by



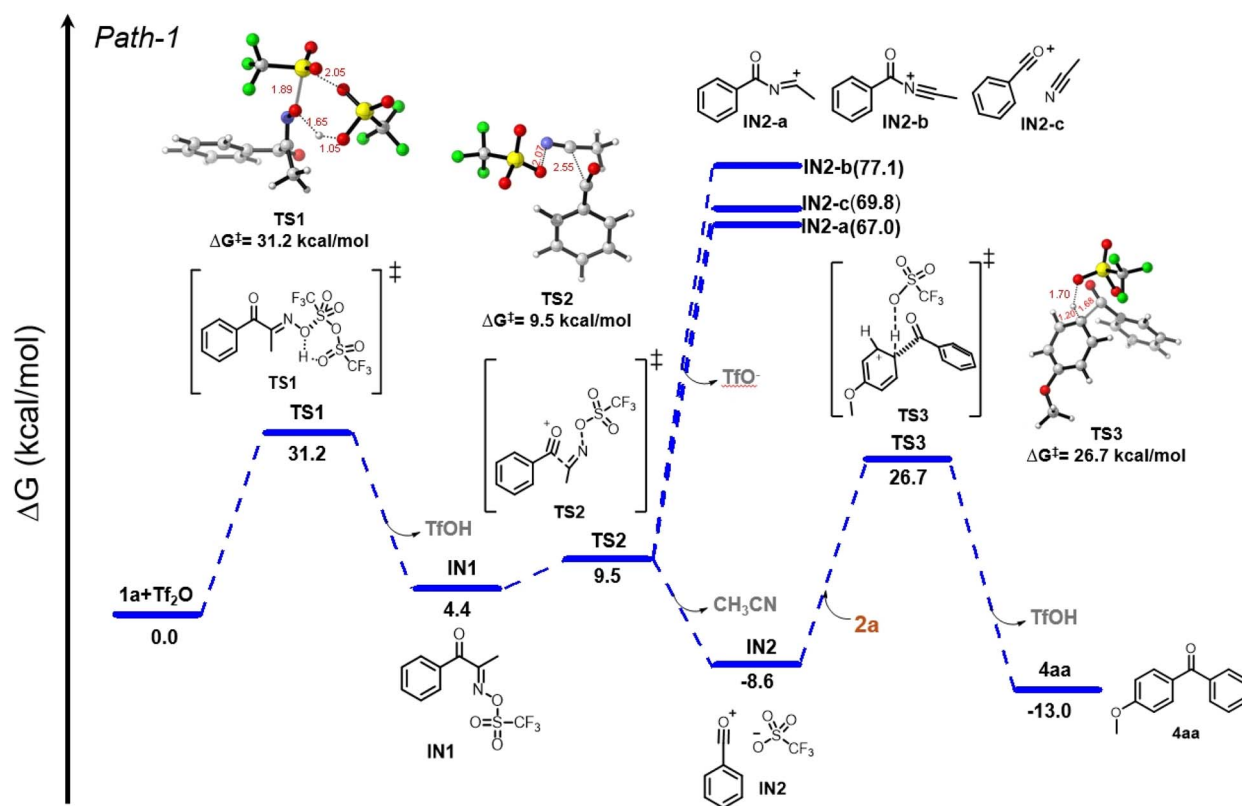
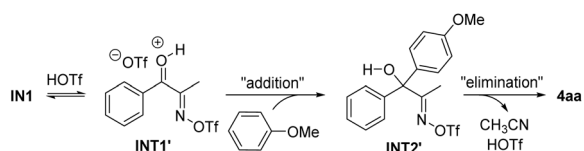


Fig. 1 DFT reaction pathway (Path-1) for the Friedel–Crafts acylation of **1a** with Tf_2O performed at the B3LYP/6-31G(d)//M06-2X/6-31G(d) level theory. The pathway includes three transition states associated with the acylation pathway. Energies are in kcal mol^{-1} .

fragmentation, is also considered. The corresponding energies are $67.0 \text{ kcal mol}^{-1}$ for **IN2-a** ($\text{C}(\text{=O})\text{-N}=\text{C}^+\text{-CH}_3$), $77.1 \text{ kcal mol}^{-1}$ for **IN2-b**, and $69.8 \text{ kcal mol}^{-1}$ for **IN2-c**. The high energies of these species suggest that they are not favorable intermediates formed after the oxime-activation of **1a**. Taken together, the formation of acylium ions through C–N fragmentation of BKR intermediates is less likely. Following the lower energy pathway, **IN2** undergoes an electrophilic aromatic substitution with anisole (**2a**) via **TS3**, where a new C–C bond forms (1.68 \AA), the aryl C–H bond elongated (1.20 \AA), and new O–H bond (1.70 \AA) forms with TfO^- acting as a base. This leads to the formation of the final product **4aa**, with a net free energy of $-13.0 \text{ kcal mol}^{-1}$, indicating thermodynamically favorable reaction.

We also considered an alternative pathway involving an addition–elimination process from **INT1'** (Scheme 5). However, based on the DFT calculation results, this pathway appears impractical due to the even higher activation free energies compared to Path 1. A detailed description of this pathway is summarized in the Fig. S1 (see the SI). The DFT study was

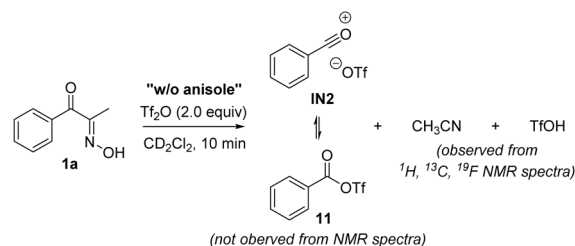


Scheme 5 Purported alternative pathway.

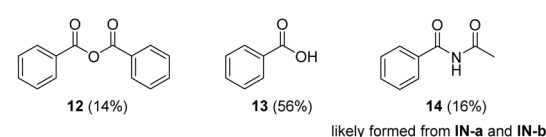
further extended to investigate the reaction mechanism of the ring-opening Friedel–Crafts acylation, leading to the formation of **7a**. The energy profile for the pathway was found to be similar to that in Fig. 1, which is briefly discussed in the SI.

To further support the proposed reaction mechanism, we conducted a control experiment in the absence of anisole, which may demonstrate the resting intermediates (Scheme 6). Based on our proposal, we expected the formation of **IN2** or its equivalent **11**, together with the byproducts such as acetonitrile and triflic acid. In the spectral data obtained from *in situ* NMR experiments, we could not identify **11** by comparing with known

6A. Reaction w/o anisole and in-situ NMR studies



6B. Obtained products after aqueous work-up & chromatography



Scheme 6 Control experiments.



data.³⁷ However, we clearly observed the formation of acetonitrile as a byproduct, which supports C_{sp²}-C_{sp²} cleavage. Notably, no other major peaks corresponding to the chemical shifts of allylic C-Hs were not observed. Additionally, after work-up and chromatographic separation of the reaction mixture, benzoic anhydride **12**, and a mixture of benzoic acid **13** and imide **14** were isolated. The formation of **12** and **13** is probably derived from **IN2** and water in the absence of anisole, whereas **14** likely came from two resonance forms, **IN-a** or **IN-b**.

However, based on the fact that the formation of **14** was negligible when running the reaction in the presence of anisole, the formation **IN-a** or **IN-b** in this control experiment is not likely derived from the Beckmann rearrangement of **1a**, but from fragmentation followed by the addition of acetonitrile to the acylium ions. Combining the DFT calculation, spectroscopic data, and results from the control experiments, we identified C-C fragmentation as a major pathway when treating **1a** with Tf₂O. Despite the unsuccessful direct observation of acylium ion pair **1N2** or **11**, based on isolated products, we tentatively conclude that the formation of **1N2** via BKF is dominant over BKR.

Conclusions

In conclusion, we have developed a novel method for FC acylation by proposing unconventional acylium precursors, α -oximinoketones. These compounds are generally stable and easy-to-handle solids, making them more user-friendly compared to traditional sources such as acyl chlorides and anhydrides. The reaction was simply operated under mild conditions using triflic anhydride for activating oxime hydroxyl group. Most of electron-rich arenes were added at ambient temperature, while near electron-neutral arenes required increasing temperature. A wide range of ketone substituents including aliphatic and aromatic moieties were tolerated as to be used as acylation sources. Additionally, cyclic α -oximinoketones can be employed for ring-opening FC acylation. This approach does not require strained systems, thereby broadening the scope and applicability of the reaction. Finally, we demonstrated the major reaction pathway using DFT calculations. The energy calculations of the mechanistically viable transition states and intermediates support the reaction pathway involving oxime activation, the generation of acylium ions through a concerted dissociation of the N-OTf group, and the addition of arenes to acylium ions. Control experiments were conducted to further support the BKF process as the major pathway of the reaction over BKR.

Author contributions

All authors have approved the final version of the manuscript. Conceptualization and supervision, H. N. Lim; methodology, analysis, data curation, Y. Shin and E. Kamaraj; writing – review and editing, Y. Shin, E. Kamaraj, and H. N. Lim; project administration, H. N. Lim; funding acquisition, H. N. Lim.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: reaction optimizations, experimental procedures and characterization data. See DOI: <https://doi.org/10.1039/d5sc08429f>.

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References

- (a) A. Friedel, J. Crafts and E. Ador, *Ber. Dtsch. Chem. Ges.*, 1877, **10**, 1854–1858; (b) C. Friedel and J. M. Crafts, *Compt. Rend.*, 1877, **84**, 1450–1454; (c) P. H. Gore, *Chem. Rev.*, 1955, **55**, 229–281; (d) H. Heaney, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, UK, 1991, vol. 2, pp. 733–752; (e) G. A. Olah, *Friedel-Crafts and Related Reactions*, Wiley-Interscience, New York, 1964, vol. 3; (f) G. A. Olah, *Friedel-Crafts Chemistry*, Wiley-Interscience, New York, 1st edn, 1973.
- (a) M. M. Heravi, V. Zadsirjan, P. Saedi and T. Momeni, *RSC Adv.*, 2018, **8**, 40061–40163; (b) A. Sumita and T. Ohwada, *Molecules*, 2022, **27**, 5984.
- Y. Nishimoto, S. A. Babu, M. Yasuda and A. Baba, *J. Org. Chem.*, 2008, **73**, 9465–9468.
- A. Wrona-Piotrowicz, D. Cegliński and J. Zakrzewski, *Tetrahedron Lett.*, 2011, **52**, 5270–5272.
- S. P. Chavan, S. Garai, A. K. Dutta and S. Pal, *Eur. J. Org. Chem.*, 2012, **2012**, 6841–6845.
- (a) G. A. Olah, N. Hartz, G. Rasul, A. Burrichter and G. K. S. Prakash, *J. Am. Chem. Soc.*, 1995, **117**, 6421–6427; (b) J. P. Hwang, G. K. Surya Prakash and G. A. Olah, *Tetrahedron Lett.*, 2000, **56**, 7199–7203.
- F. Guo, J. Xiao, J. Deng, F. Li and Z.-L. Tang, *ChemistrySelect*, 2022, **7**, e202103691.
- K. W. Anderson and J. J. Tepe, *Org. Lett.*, 2002, **4**, 459–461.
- (a) D. A. Klumpp, R. Rendy, Y. Zhang, A. Gomez and A. McElrea, *Org. Lett.*, 2004, **6**, 1789–1792; (b) E. K. Raja, D. J. DeSchepper, S. O. N. Lill and D. A. Klumpp, *J. Org. Chem.*, 2012, **77**, 5788–5793.
- Y. Liu, G. Meng, R. Liu and M. Szostak, *Chem. Commun.*, 2016, **52**, 6841–6844.
- N. Yonezawa, T. Hino, T. Kinuno, T. Matsuki and T. Ikeda, *Synth. Commun.*, 1999, **29**, 1687–1695.
- Y. Zhang, L. Sun, Z. Xu, T. Tan and Z. Wang, *Org. Lett.*, 2024, **26**, 6164–6168.
- E. Louïse, *Ann. Chim. Phys.*, 1885, **6**, 174.
- R. C. Fuson, G. R. Barker and B. Vittimberga, *J. Am. Chem. Soc.*, 1959, **81**, 4858–4860.
- T. Keumi, T. Morita, T. Shimada, N. Teshima and H. Kitajima, *J. Chem. Soc., Perkin Trans. 2*, 1986, 847–852.



- 16 J. R. Frost, C. B. Cheong, W. M. Akhtar, D. F. Caputo, N. G. Stevenson and T. J. Donohoe, *J. Am. Chem. Soc.*, 2015, **137**, 15664–15667.
- 17 J. R. Carson and N. M. Davis, *J. Org. Chem.*, 1981, **46**, 839–843.
- 18 For acyl chlorides, see: (a) D. Milstein and J. K. Stille, *J. Org. Chem.*, 1979, **44**, 1613–1618; (b) E.-I. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller and A. T. Stoll, *Tetrahedron Lett.*, 1983, **24**, 5181–5184; (c) D. Lee, T. Ruy, Y. Park and P. H. Lee, *Org. Lett.*, 2014, **16**, 1144–1147; (d) A. D. Benischke, M. Leroux, I. Knoll and P. Knochel, *Org. Lett.*, 2016, **18**, 3626–36263629; (e) J. Zhang, P. Zhang, Y. Ma and M. Szostak, *Org. Lett.*, 2022, **24**, 2338. For anhydrides, see: (f) L. J. Gooßen and K. Ghosh, *Angew. Chem., Int. Ed.*, 2001, **40**, 3458–3460. For acyl fluorides, see: (g) Y. Zhang and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 15964–15965; (h) Y. Ogiwara, Y. Maegawa, D. Sakino and N. Sakai, *Chem. Lett.*, 2016, **45**, 790–792; (i) Y. Ogiwara, D. Sakino, Y. Sakurai and N. Sakai, *Eur. J. Org. Chem.*, 2017, **2017**, 4324–4327; (j) J. Reimler, X.-Y. Yu, N. Spreckelmeyer, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303222. For esters and amides, see: (k) R. Takise, K. Muto and J. Yamaguchi, *Chem. Soc. Rev.*, 2017, **46**, 5864–5888; (l) G. Li and M. Szostak, *Chem. Rec.*, 2020, **20**, 649–659; (m) Y. Goto, M. Sano, Y. Sumida and H. Ohmiya, *Nat. Synth.*, 2023, **2**, 1037–1045. For thioesters, see: (n) L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, 2000, **122**, 11260–11261; (o) Y.-F. Li, Y.-F. Wei, J. Tian, J. Zhang, H.-H. Chang and W.-C. Gao, *Org. Lett.*, 2022, **24**, 5736–5740. For aldehydes, see: (p) J. Ruan, O. Saidi, J. A. Iggo and J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 10510–10511; (q) X. Zhang and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2017, **139**, 11353–11356; (r) L. Wang, T. Wang, G.-J. Cheng, X. Li, J.-J. Wei, B. Guo, C. Zheng, G. Chen, C. Ran and C. Zheng, *ACS Catal.*, 2020, **10**, 7543–7551; (s) P. Fan, C. Zhang, L. Zhang and C. Wang, *Org. Lett.*, 2020, **22**, 3875–3878; (t) F. Wang, B. Wang, Q. Wang and L. Wang, *Eur. J. Org. Chem.*, 2025, **28**, e202401206. For acylsilanes, see: (u) S. D. Ramgren and N. K. Garg, *Org. Lett.*, 2014, **16**, 824–827. For ketoacids, see: (v) D.-L. Zhu, Q. Wu, D. J. Young, H. Wang, Z.-G. Ren and H.-X. Li, *Org. Lett.*, 2020, **22**, 6832–6837; (w) M. He, X. Yu, Y. Wang, F. Li and M. Bao, *J. Org. Chem.*, 2021, **86**, 5016–5025; (x) X. Kong, Y. Chen, X. Chen, Z.-X. Lu, W. Wang, S.-F. Ni and Z.-Y. Cao, *Org. Lett.*, 2022, **24**, 2137–2142.
- 19 (a) J. Wang, W. Chen, S. Zuo, L. Liu, X. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 12334–12338; (b) Y. Xia, J. Wang and G. Dong, *J. Am. Chem. Soc.*, 2018, **140**, 5347–5351.
- 20 T. Matsuda, M. Makino and M. Murakami, *Org. Lett.*, 2004, **6**, 1257–1259.
- 21 R. Talukdar, *Synthesis*, 2020, **52**, 3764–3780.
- 22 (a) J. L. Holmes, L. Almeida, B. Barlaam, R. A. Croft, A. P. Dishington, L. Gingipalli, L. A. Hassall, J. L. Hawkins, S. Ioannidis, J. W. Johannes, T. M. McGuire, J. E. Moore, A. Patel, K. G. Pike, T. Pontz, X. Wu, T. Wang, H.-J. Zhang and X. Zheng, *Synthesis*, 2016, **48**, 1226–1234; (b) T. H. Hsieh, P. Y. Liao, Y. T. Liu, C. H. Wang, C. C. Lin and T. C. Chien, *J. Chin. Chem. Soc.*, 2018, **65**, 325–330.
- 23 (a) X. Meng, D. Chen, R. Liu, P. Jiang and S. Huang, *J. Org. Chem.*, 2021, **86**, 10852–10860; (b) T. Masek and U. Jahn, *J. Org. Chem.*, 2021, **86**, 11608–11632.
- 24 T. Fu, S. Zhu, X. Zhao and S. Huang, *Green Chem.*, 2022, **24**, 6849–6853.
- 25 M. Kataoka and M. Ohno, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 3474–3477.
- 26 S. E. Lee, Y. Kim, Y. H. Lee and H. N. Lim, *Org. Lett.*, 2024, **26**, 3646–3651.
- 27 D. Kim and H. N. Lim, *Org. Lett.*, 2020, **22**, 7465–7469.
- 28 The initially obtained products contained O-trifluoromethylsulfonyl enol ethers of **4ar** as major side products. After desulfonylation under basic conditions, two regioisomers were purified by chromatographic separation.
- 29 α -Oximation of ketones was achieved using the well-established procedures. For acid-assisted oximation of ketones, see: (a) A. F. Ferris, *J. Org. Chem.*, 1959, **24**, 1726–1730; (b) W. L. Semon and V. R. Damerell, *Org. Syn.*, 2003, **10**, 22. For base-assisted oximation of ketones, see: (c) F. H. Stodola, E. C. Kendall and B. F. Mckenzie, *J. Org. Chem.*, 1941, **6**, 841–844; (d) M. Schlegel and C. Schneider, *Org. Lett.*, 2018, **20**, 3119–3123. For condensation between hydroxylamine and 1,2-diketones, see: (e) H. Rapoport and A. R. Williams, *J. Am. Chem. Soc.*, 1949, **71**, 1774–1778; (f) A. R. Katritzky, Z. Wang, C. D. Hall, N. G. Akhmedov, A. A. Shestopalov and P. J. Steel, *J. Org. Chem.*, 2003, **68**, 9093–9099. For nitrosation of silyl enol ethers, see: (g) M. Baidya and H. Yamamoto, *J. Am. Chem. Soc.*, 2011, **133**, 13880–13882.
- 30 Acetylation was achieved with commercially available diacetylmonoxime **2b**. However, propanoylation, isobutanoylation, and pivaloylation were performed using structurally different types of α -oximinoketones. For the structures of these acylation sources, see the SI.
- 31 For detailed optimization studies, see the SI.
- 32 (a) M. G. Davlieva, S. V. Lindeman, I. S. Neretin and J. K. Kochi, *New J. Chem.*, 2004, **28**, 1568–1574; (b) M. B. Smith and J. March, *March's Advanced Organic Chemistry*, Wiley, 6th edn, 2007.
- 33 K. Padala and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144–6147.
- 34 A detailed description of the computational methods is provided in the SI.
- 35 S. Zhang, M. Vayer, F. Noël, V. D. Vuković, A. Golushko, N. Rezajooei, C. N. Rowley, D. Leboef and J. Moran, *Chem*, 2021, **7**, 3245–3441.
- 36 M.-T. T. Nguyen, N. Le, H. T. Nguyen, T. D. V. Luong, V. K. T. Nguyen, Y. Kawazoe, P. H. Tran and N.-N. Pham-Tran, *ACS Omega*, 2023, **8**, 271–278.
- 37 (a) R. G. Kinney and B. A. Arndtsen, *Angew. Chem., Int. Ed.*, 2019, **58**, 5085–5089; (b) A. Hermannsdorfer and M. Driess, *Angew. Chem., Int. Ed.*, 2021, **60**, 13656–13660.

