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Divergent Reactivity of *gem*-Difluoro-enolates toward Nitrogen Electrophiles: Unorthodox Nitroso Aldol Reaction for Rapid Synthesis of α-Ketoamides

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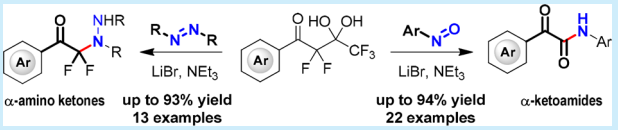
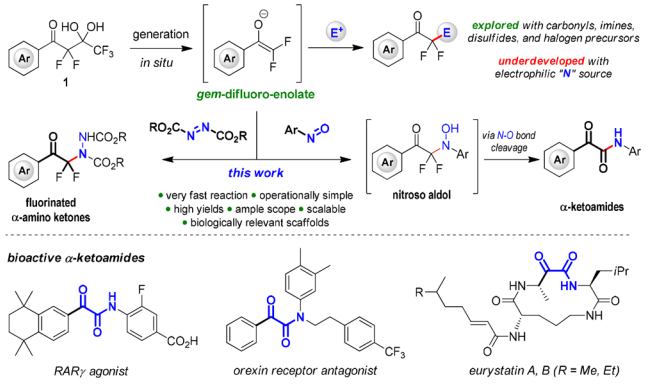
Supporting Information

ABSTRACT: An amination reaction of *in situ* generated *gem*-difluoro-enolates has been explored with electrophilic nitrogen sources. While their exposure to azodicarboxylates smoothly produced fluorinated α-amino ketones, reaction with nitrosoarenes (nitroso aldol reaction) furnished α-ketoamides in very high yields (up to 94%). The reaction is very fast (typically completed within 5 min) and scalable and tolerates various sensitive functional groups. Synthetic utility of this process was highlighted through the production of diverse nitrogen heterocycles and an orexin receptor antagonist.



With the important reputation of organofluorines in pharmaceutical science and drug discovery,[1] strategic utilization of fluoro-enolates has become a continuous enterprise in contemporary organic synthesis.[2,3] In this context, α-fluorinated *gem*-diols (**1**), recently introduced by the Colby group, are highly alluring (Scheme 1).[4,5] They are readily prepared in large quantities and offer convenient access to *gem*-difluoro-enolates under mild conditions. Currently, aldol, Mannich, halogenation, and sulfenylation processes of these *in situ* generated fluoro-enolates have been explored.[6,7] However, systematic investigation with electrophilic aminating agents that could potentially offer fluorinated α-amino ketones, a high-value synthon and novel structural motif, remains underdeveloped.

Scheme 1. Reactions of *gem*-Difluoro-enolates and Bioactive α-Ketoamides



Among the various nitrogen electrophiles, nitrosoarenes and azodicarboxylates are the most used.[8,9] They are bench-stable reagents and widely available in great structural varieties. However, in comparison to azodicarboxylates, utilization of nitrosoarenes for the C−N bond forming process is increasingly challenging because they are prototypes of ambident electrophiles. The reaction can proceed via oxygen (*O*-nitroso aldol) and nitrogen centers (*N*-nitroso aldol), leading to a mixture of regioisomeric products.[8,10] Meanwhile, in contrast to the N−N bond, the N−O bond thus formed after the reaction is more labile to cleave. Consequently, a distinct reaction outcome might be realized under judicial reaction conditions. Herein, we report our findings on divergent reactivity of *in situ* generated *gem*-difluoro-enolates toward nitrosoarenes and azodicarboxylates. While reactions of azodicarboxylates straightforwardly delivered difluorinated α-amino ketones, corresponding reactions with nitrosoarenes offered α-ketoamides (Scheme 1). Notably, α-ketoamides are privileged structural frameworks found in various bioactive compounds and natural products (Scheme 1),[11] and devising new strategies for their synthesis is desired.

At the outset, we examined the reaction of α-fluorinated *gem*-diols **1a**, a precursor for the *in situ* generation of *gem*-difluoro-enolate, with commercially available nitrosobenzene **2a** (Table 1). A mixture of **1a** and **2a** in acetonitrile was exposed to a 20 mol % $Cu(OTf)_2$/bipyridine complex in the presence of NEt_3 base at room temperature (Table 1, entry 1). While both the starting materials were consumed within 3 h, an intent analysis of the reaction mixture revealed the absence of the desired nitroso aldol product. Instead, a rearranged product, α-ketoamide **3a**, was isolated in 30% yield along with ketone **3a′** that was formed via protonation of the *in situ* generated *gem*-difluoro-enolate. Encouraged by this serendipitous result, screening of various metal catalysts in combination with nitrogen-centered ligands was investigated (entries 2−8).

However, most of these conditions were ineffective to produce α-ketoamide. A major breakthrough came when LiBr

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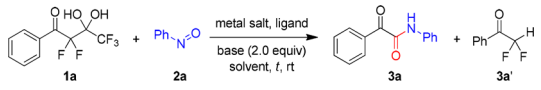
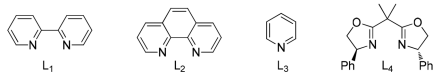
Table 1. Development of Nitroso Aldol Reaction with *gem*-Difluoro-enolate Generated *in Situ* from the Precursor 1a[a]



entry	solvent	metal salt (equiv) / ligand (equiv)	base	*t*	yield of **3a** (%)[b]
1	CH_3CN	$Cu(OTf)_2$ (0.2) / L_1 (0.2)	Et_3N	3 h	30[c]
2	CH_3CN	CuTc (0.2) / L_1 (0.2)	Et_3N	3 h	–[c]
3	CH_3CN	$Cu(CH_3CN)_4{\cdot}BF_4$ (0.2) / L_1 (0.2)	Et_3N	3 h	–[c]
4	CH_3CN	$Sc(OTf)_3$ (0.2) / L_1 (0.2)	Et_3N	3 h	–[c]
5	CH_3CN	$Yb(OTf)_3$ (0.2) / L_1 (0.2)	Et_3N	3 h	–[c]
6	CH_3CN	$Cu(OTf)_2$ (0.2) / L_2 (0.2)	Et_3N	3 h	26[c]
7	CH_3CN	$Cu(OTf)_2$ (0.2) / L_3 (0.2)	Et_3N	3 h	33[c]
8	CH_3CN	$Cu(OTf)_2$ (0.2) / L_4 (0.2)	Et_3N	3 h	–[c]
9	CH_3CN	LiBr (1.0)	Et_3N	20 min	42
10	CH_3CN	LiBr (2.0)	Et_3N	20 min	68
11	**CH_3CN**	**LiBr (3.0)**	**Et_3N**	**5 min**	**92**
12	CH_3CN	LiBr (3.0)	K_3PO_4	3 h	23
13	CH_3CN	LiBr (3.0)	Na_2CO_3	3 h	–[d]
14	CH_3CN	LiBr (3.0)	$NaHCO_3$	3 h	–[d]
15	THF	LiBr (3.0)	Et_3N	5 min	51
16	dioxane	LiBr (3.0)	Et_3N	5 min	36
17	DCE	LiBr (3.0)	Et_3N	5 min	–[c]
18	CH_3CN	LiBr (3.0)	–	3 h	–[d]
19	CH_3CN	–	Et_3N	3 h	–[c]

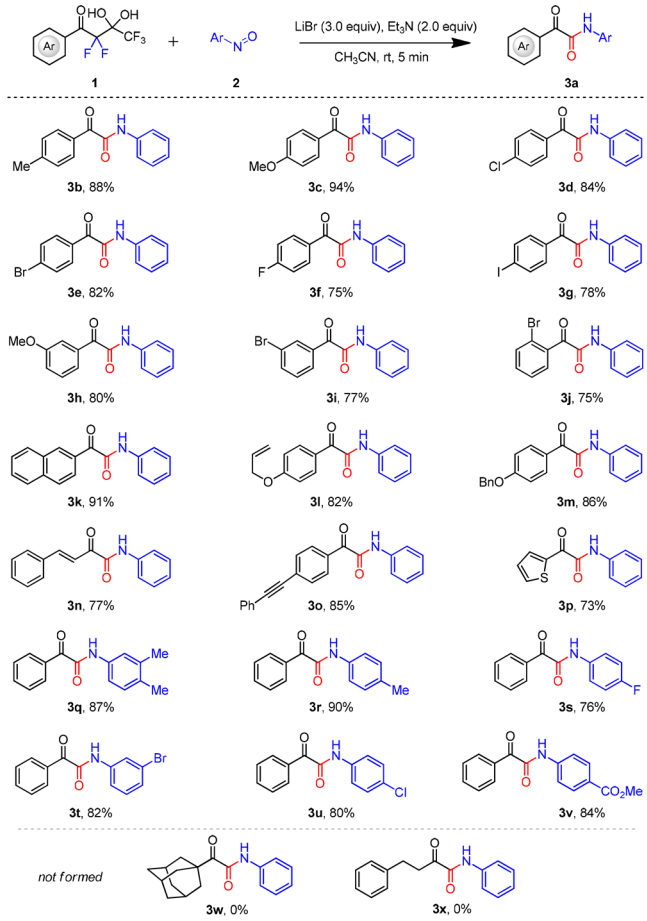


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), metal salt, base (2.0 equiv), solvent (4 mL). [b]Isolated yield. [c]Decomposition of **1a** was observed with the formation of **3a′**. [d]No reaction with the recovery of **1a**.

(1 equiv) in the presence of NEt_3 was employed, delivering the product **3a** in 42% yield within 20 min (entry 9). Further increase of LiBr loading improved the reaction yield, shortening the reaction time, and the best result was obtained with 3 equiv of LiBr, offering α-ketoamide **3a** in 92% yield in 5 min (entry 11). Screening of other bases (entries 12–14) and solvents (entries 15–17) gave inferior results. Control experiments demonstrated that the presence of both LiBr and NEt_3 was crucial for this process, and the reaction was completely shut down in the absence of either of them (entries 18–19).

Having identified the optimal reaction conditions, we then investigated the scope of the methodology (Scheme 2). The reaction is very general. A wide range of *gem*-diols (**1**) having

Scheme 2. Scope of *gem*-Diols and Nitrosoarenes in α-Ketoamide Synthesis[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), LiBr (3.0 equiv), NEt_3 (2.0 equiv), CH_3CN (4 mL), 5 min. Isolated yield.

electron-donating substitutions (**3b–c**, **3h**) and various halogen functionalities such as chloro (**3d**), bromo (**3e**, **3i–j**), iodo (**3g**), and fluoro (**3f**) at *para*-, *meta*-, and *ortho*-positions smoothly reacted under the optimized conditions to deliver the desired products in very high yields (75–94%). A naphthyl-substituted *gem*-diol generated the product **3k** in 91% yield. This protocol demonstrated good functional group compatibility: allyl (**3l**), benzyl (**3m**), styryl (**3n**), and alkyne (**3o**) groups were well-tolerated. Interestingly, a *gem*-diol containing a heterocyclic aromatic thiophene ring furnished the product **3p** in 73% isolated yield.

The scope of nitrosoarenes (**2**) was also explored (Scheme 2). Satisfyingly, various electron-rich (**3q–r**) and electron-deficient (**3s–v**) nitrosoarenes effectively participated in the reaction and uniformly afforded the desired α-ketoamides in good to excellent yields (76–90%).

The alkyl derivatives of α-fluorinated *gem*-diols were not suitable substrates for this process, and the desired α-ketoamides **3w–x** were not formed when adamantyl- and homobenzyl-substituted *gem*-diols were examined under the optimized reaction conditions (Scheme 2).

To explore the reactivity of *gem*-difluoro-enolates further, the reaction of *gem*-diol (**1**) with azodicarboxylate (**4**) was investigated (Scheme 3).[12] Gratifyingly, when azodicarboxylate **4a** was reacted with the *gem*-difluoro-enolate generated *in situ* from *gem*-diol **1a** under the conditions optimized for the

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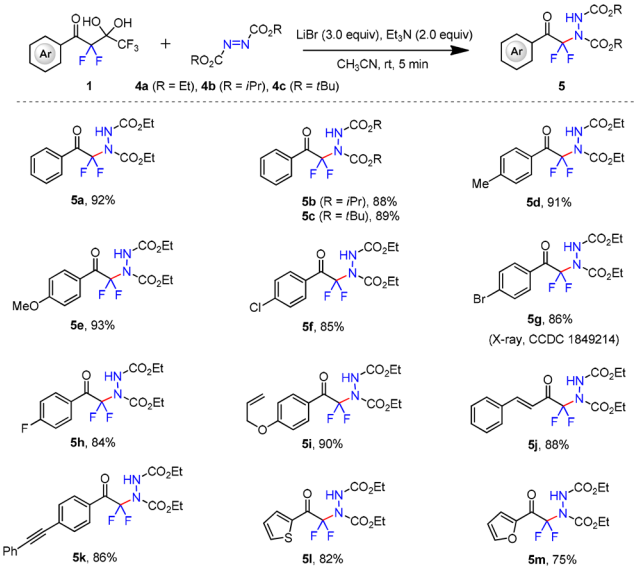
Scheme 3. Scope of *gem*-Diols and Azodicarboxylates in α-Amination of *gem*-Difluoro-enolates[a]

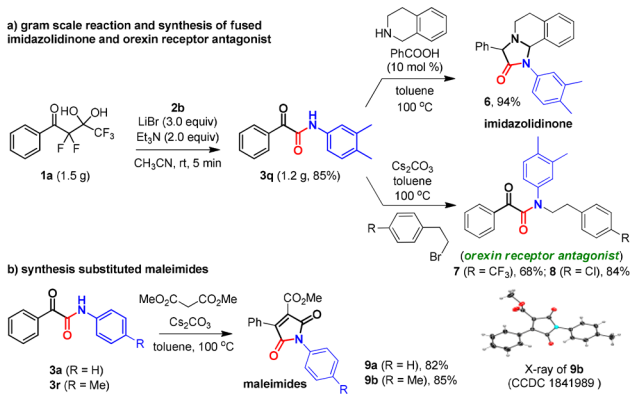


[a]Reaction conditions: **1** (0.3 mmol), **4** (0.36 mmol), LiBr (3.0 equiv), NEt_3 (2.0 equiv), CH_3CN (4 mL), 5 min. Isolated yield.

nitrosoarenes, a difluoro-substituted α-amino ketone **5a** was formed in 92% yield. Here, the formation of α-ketoamide, as observed in the case of nitrosoarenes, was not detected. This significantly different reaction output could be attributed to the stability of the N−N bond compared to facile cleavage of the N−O bond under the reaction conditions. Notably, this α-amination process displayed a broad substrate scope with high reaction yields (75−93%) and accommodated various sensitive functional groups, including olefins (**5i**−**j**), alkyne (**5k**), and heterocycles (**5l**−**m**).

To evaluate the efficacy of the α-ketoamide synthesis, a gram-scale reaction was performed, and the product **3q** was obtained in 85% yield (Scheme 4a). Also, these α-ketoamide

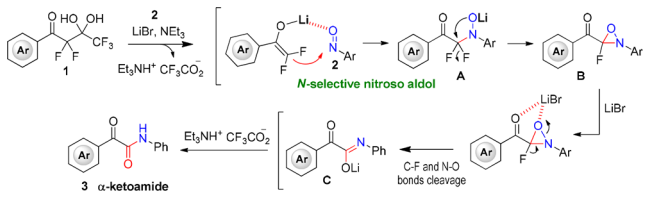
Scheme 4. Synthetic Applications of α-Ketoamides



products exhibited versatile reactivity. Treatment of **3q** with 1,2,3,4-tetrahydroisoquinoline in the presence of benzoic acid as catalyst at 100 °C furnished the imidazolidinone derivative **6** in 94% yield.[13] Further, compound **7** which is a known orexin receptor antagonist[11a,f] and its derivative **8** have been synthesized in high yields via base-mediated N-substitution of α-ketoamide **3q** with trifluoromethyl and chloro-substituted homobenzyl bromides, respectively (Scheme 4a). When α-ketoamides **3a** and **3r** were independently exposed to dimethyl malonate in the presence of Cs_2CO_3 at 100 °C, the highly substituted maleimides **9a** and **9b** were formed in 82% and 85% yields, respectively (Scheme 4b).

While a comprehensive study detailing mechanistic clarification awaits further investigations, the plausible pathway is depicted in Scheme 5. The *gem*-difluoro-enolate generated

Scheme 5. Plausible Reaction Mechanism for the Formation of α-Ketoamides



from the precursor **1** in the presence of LiBr and NEt_3 reacts with nitrosoarene **2** and produces intermediate **A**. Here, the N-selective nitroso aldol reaction is expected, as the oxygen center of the nitroso compound will be involved in coordination with the oxophilic lithium metal, leaving the N-center free for the aldol process. Intermediate **A** then undergoes intramolecular nucleophilic substitution to afford the intermediate **B**, which upon activation with LiBr rearranges to intermediate **C** via C−F and N−O bond cleavage. Finally, protonation of the intermediate **C** delivers the desired product α-ketoamide **3**. As a significant amount of product **3a** was formed in the presence of $Cu(OTf)_2$ (Table 1) and the triflate anion is a putative non-nucleophilic counterion, the product formation via C−F/N−O bond cleavage through nucleophilic attack of the bromide ion onto the fluoride atom in the intermediate **B** is quite unlikely.

In conclusion, divergent reactivity of *gem*-difluoro-enolates, generated *in situ* from the readily available difluorinated *gem*-diols (**1**) in the presence of LiBr and NEt_3, has been demonstrated based on electrophilic amination reactions. The use of readily available nitrosoarenes as an electrophilic nitrogen source resulted in an N-selective nitroso aldol reaction followed by a cascade rearrangement to furnish α-ketoamides in excellent yields. Under identical reaction conditions, azodicarboxylates produced a series of difluoro-substituted α-amino ketones. Both reactions proceed very rapidly at room temperature (usually 5 min) and display very broad substrate scope with high functional group compatibility. The synthetic utility of this protocol has been showcased in the synthesis of diverse heterocyclic frameworks and an orexin receptor antagonist. Further applications of *gem*-difluoro-enolates in organic synthesis are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01900.

Complete experimental details and characterization data for the prepared compounds (PDF)

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Accession Codes

CCDC 1841989 and 1849214 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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