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Stereoselective three-component cascade synthesis of α-substituted 2,4-dienamides from *gem*-difluorochloro ethanes†

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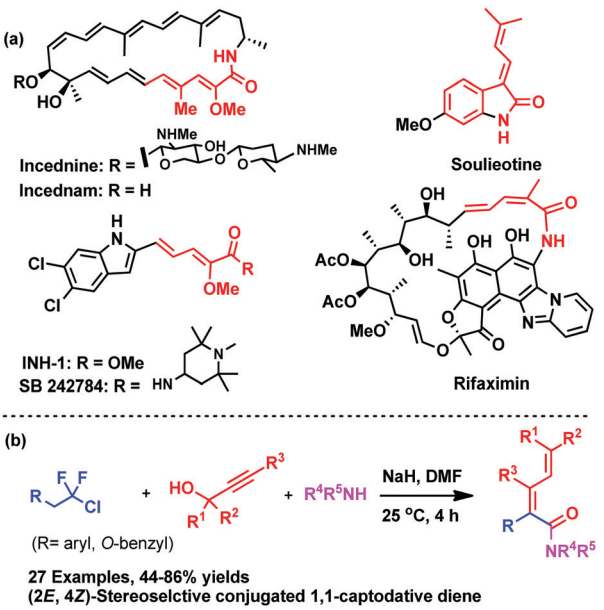
Herein, we describe a new transition metal-free Claisen rearrangement for the synthesis of α-substituted 2,4-dienamides. The one-pot, stereoselective three-component cascade reaction between a series of propargyl alcohols, amines, and *gem*-difluorochloro ethane derivatives afforded various polysubstituted 2,4-dienamides in good yields. This synthetic method for 1,1-captodative dienes, α-substituted 2,4-dienamides, can be utilized for preparing pharmaceutical analogues containing an indolin-2-one or lactone moiety.

Diverse dienes with stereogenic centers are found in a myriad of natural products and as notable pharmaceuticals and agrichemicals (Scheme 1).[1] Various types of diene scaffolds are widely used as building blocks in a broad range of organic reactions (*e.g.*, cascade, Friedel–Crafts, polymerization, and cycloaddition reactions).[2] Although polysubstituted diene synthesis has been widely used in various fields, 1,1-captodative dienes, which contain both the amide residue (captor group) and an alkyloxy or aryl group (dative group), are rare, because efficient and facile access to them is somewhat challenging. Furthermore, the diverse substitution not only at the α-position but also at the β-position of 1,1-captodative dienes (*i.e.*, α-substituted dienamide) has an important role for controlling the polymerization and cycloaddition reaction by tuning the electron density.[3] Therefore, the stereoselective synthesis of 1,1-captodative dienes and a versatile scaffold containing both the donor (alkoxy) and acceptor (amide) groups is highly desirable.

The synthesis of α-substituted dienamides is well addressed in terms of transition metal-catalyzed cross coupling reaction, olefinic metathesis, or C–H activation.[4] Conversely, a metal-free steroselective synthesis of dienamides is still challenging. Conventionally, Wittig and Horner–Wadsworth–Emmons reactions are used for the synthesis of (*Z*)- or (*E*)-selective dienamides using α,β-unsaturated aldehydes in the presence of a strong base. However, a multistep reaction is required for the functional group manipulation.[5] Such reactions are also restricted because of the sensitive aldehyde group (which may also be generated *in situ* during reaction) that is vulnerable under strong basic conditions.

Although there are two previous reports on the one-step synthesis of α-alkoxy dienamides,[6,7] both the approaches require either a chiral moiety/strong base or the unstable isocyanate for preparing the α-alkoxy dienamide analogues. Other methods for synthesizing dienamides include Ficini–Claisen and Eschenmoser–Claisen rearrangements. These rearrangements proceed *via* an



Scheme 1 Representative natural products and drug molecules (a) and synthesis of α-substituted 2,4-dienamides (b, present work).

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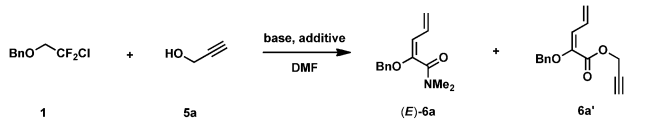
allene intermediate that is converted from propargylic alcohol. However, these methods have several limitations, such as the requirement of high temperature, strong base, unstable ynamine reactant, and self-migration before rearrangement.[8,9] Therefore, a straight forward, simple, and milder approach for the synthesis of α-substituted 2,4-dienamide from easily available starting materials is needed. Herein, we report the stereoselective metal-free synthesis of α-substituted 2,4-dienamides, involving the *in situ* generation of vinyl propargylic ether *via* the reaction of *gem*-difluorochloro ethane derivatives and propargyl alcohols. To the best of our knowledge, this is the first report on the synthesis of α-substituted 2,4-dienamides from the easily available *gem*-difluorochloro ethane derivatives.

Two *gem*-difluoro halide ethane derivatives, 1,1-difluoro-1-chloro-2-benzyloxy ethane (**1**) and 1,1-difluoro-1-bromo-2-benzyloxy ethane, were prepared from methyl chloro difluoroacetate (MCDFA) and ethyl bromo difluoroacetate (EBDFA), respectively.[10] To find the optimal reaction conditions for the synthesis of (*E*)-**6a**, the reaction was carried out in the presence of various bases, additives, diverse solvents, and reaction temperatures (Table 1). By increasing the temperature, the desired dienamide (*E*)-**6a** was obtained in 15% yield. The presence of additional 18-crown-6 enhanced the yield, although the minor product, ester **6a′**, was also generated in 8% yield. (Table 1, entries 1–3). In addition to K_2CO_3 and Cs_2CO_3, relatively strong bases such as LiOEt, LiHMDS, KO^{t}Bu, and NaOH, as well as metals like, Zn and Ag_2O were used.[11–13] However, these are not effective in this transformation. Further screening of the base indicated that 2 equiv. of NaH solely generated the side product **6a′**. Under the same reaction conditions, the yield of (*E*)-**6a** was dramatically increased to 62% upon the addition of Me_2NH (Table 1, entries 6 and 7). The yield slightly decreased to 55% in the absence of Me_2NH in DMF (Table 1, entry 9).[14] To confirm the role of Me_2NH, the reaction between **1** (1 equiv.) and **5a** (1.2 equiv.) was performed in the presence of NaH (2 equiv.) in DMF-d_7. Though the yield was decreased to 44%, the isolated deuterated product (*E*)-**6a**-d_6 showed 100% incorporation of deuterium, as evident from the ^{1}H NMR spectrum (ESI,† 1.3.) The same reaction in the presence of 3 equiv. of Me_2NH resulted in a comparatively better yield (56%). However, only 13% incorporation of deuterium was observed. This indicates that the absence of an external amine source (R^4R^5NH) curtails the yields, because the reactive intermediate may decompose in the reaction medium and/or lower the availability of Me_2NH.

Table 1 Optimization of dienamide synthesis[a]



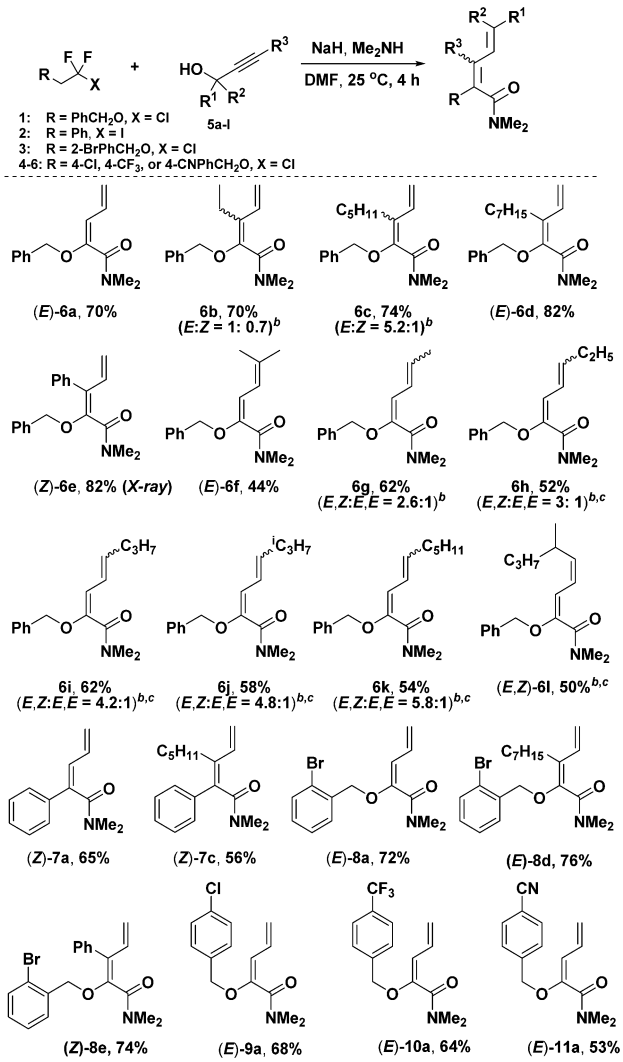
1 5a (*E*)-6a 6a'

Entry	Base	Additive[b]	T (°C)	Time (h)	Yield[c] (%) (*E*)-**6a**	**6a′**
1	K_2CO_3	—	25	8	Trace	—
2	K_2CO_3	—	60	8	15	—
3	K_2CO_3	18-crown-6	60	8	23	8
4	Cs_2CO_3	18-crown-6	60	8	30	10
5	Cs_2CO_3	18-crown-6	100	8	Trace	Trace
6[d]	NaH	—	25	4	—	22
7[d]	NaH	Me_2NH	25	4	62	—
8[d,e]	NaH	Me_2NH	25	4	32	—
9	NaH	—	25	4	55	—
10	**NaH**	**Me_2NH**	**25**	**4**	**70**	—
11[f]	NaH	Me_2NH	25	4	40	—
12[g]	NaH	Me_2NH	25	4	46	—

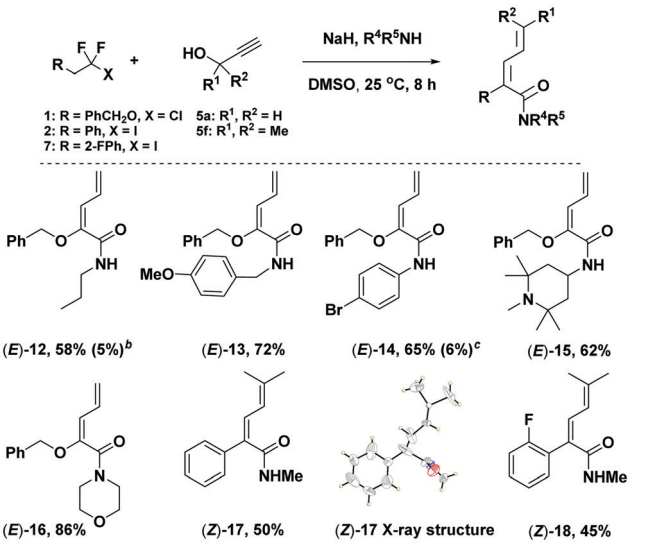
[a] All the reactions were performed on a 0.48 mmol scale of **1** (1 equiv.) and propargyl alcohol **5a** (1.2 equiv.) in DMF (3 mL). Base (2 equiv.) was added to the reaction mixture at 0 °C, and then the temperature (T) was increased. [b] 18-crown-6 (2 equiv.) or Me_2NH (3 equiv.) was used as an additive. [c] Isolated yield. [d] DMSO (3 mL) was used as the solvent. [e] NaH (1 equiv.) was used. [f] NaH (4 equiv.) was used. [g] 1,1-Difluoro-1-bromo-2-benzyloxy ethane was used.

Inspired by the initial result (Table 1, entry 2) and after screening different reaction conditions, the optimum reaction conditions for the synthesis of the desired α-aryloxy dienamide (*E*)-**6a** (70%) were found (Table 1, entry 10). However, the reaction between the corresponding *gem*-difluorobromo ethane derivative (instead of **1**) and **5a** did not increase the yield of (*E*)-**6a** (Table 1, entry 12).

To assess the scope of α-substituted 2,4-dienamide synthesis, a series of substituted propargylic alkynols were reacted with *gem*-difluoro halide ethane derivatives (**1–7**) under the optimized reaction conditions (Schemes 2 and 3). When pent-2-yn-1-ol (**5b**) was treated with a *gem*-difluorochloro ethane derivative (**1**) under the optimum reaction conditions, a mixture of (*E*/*Z*)-**6b** was obtained in 70% yield in 1 : 0.7 ratio, along with a trace amount of *gem*-difluoro propargyl ether (**19**) as the side product. The reaction with oct-2-yn-1-ol (**5c**) under the same reaction conditions led to the desired dienamides (*E*)-**6c** and (*Z*)-**6c** in 5.2 : 1 ratio. Interestingly, the more extended alkyne, dec-2-yn-1-ol (**5d**), provided the desired β-substituted dienamide (*E*)-**6d** as the sole product in 82% yield. Similarly, the bulkier aryl substituted alkynol, 3-phenyl-2-propyn-1-ol (**5e**), also gave the β-substituted dienamide (*Z*)-**6e** (due to priority) as the sole product (82%). The structure of (*Z*)-**6e** was unambiguously confirmed by the single crystal X-ray diffraction (XRD) analysis (see ESI† 3). The substrate with 2-bromo-benzyl substituent **3** also generated (*E*)-**8a,** as well as relatively complicated substrate (*E*)-**8d** and (*Z*)-**8e,** as a sole product with good yields under the optimised reaction conditions. In addition, the aryl substrates (*Z*)-**7a**, (*Z*)-**7c**, (*Z*)-**17**, and (*Z*)-**18** bearing phenyl and 2-fluoro-phenyl groups were prepared from the aryl *gem*-difluoro halides, **2** and **7**. These obtained α-aryl 2,4-dienamides can be used as intermediates to produce bioactive 3-substituted indolin-2-one analogues, which are potentially interesting in medicinal chemistry.[15] Consequently, two more *gem*-difluoroiodo ethane derivatives, 1,1-difluoro-1-iodo-2-phenyl ethane (**2**) and 1,1-difluoro-1-iodo-2-(2-fluorophenyl) ethane (**7**) were prepared in three steps.[16] Interestingly, slightly less pure **2** (>90%) reacted with **5a** and **5c** as a coupling alkyne partner, resulting in highly stereoselective 2-phenyl-(*Z*)-2,4-dienamides (*Z*)-**7a**[17a] and (*Z*)-**7c** in moderate yields, respectively. More sensitive *para*-substituted (Cl, CF_3, and CN) *gem*-difluoro chloride ethanes (**4–6**) also gave the corresponding dienamides (*E*)-**9a–11a** with good yields. Furthermore, a series of terminal alkynes (R^1 or R^2 = alkyl) were reacted with **1** to procure the corresponding products **6g–6k**. Interestingly, the isolated yield



Scheme 2 Substrate scope of α-substituted 2,4-dienamides.[a] [a]Reaction conditions: *gem*-difluorohalide ethanes (**1–6**): alkynols (**5a–l**): Me_2NH : NaH = 0.48 : 0.57 : 1.44 : 0.96 (mmol) in 3 mL DMF at 25 °C for 4 h. All the yields refer to the isolated products after column chromatography on silica gel. [b]All the ratios of (*E*), (*Z*), (*E*,*Z*), and (*E*,*Z*:*E*,*E*)-configuration were determined by ^{1}H NMR spectroscopy (see ESI†). [c]8 h of reaction time.



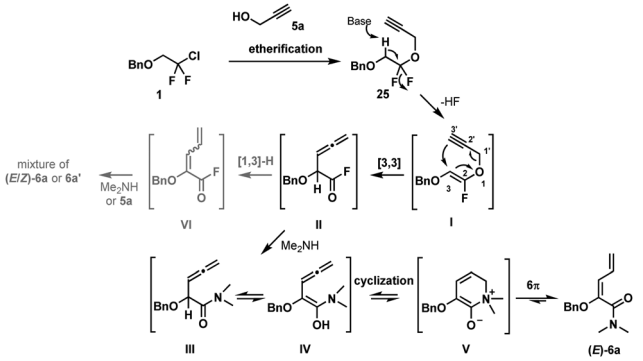
Scheme 3 Substrate scope for α-substituted 2,4-dienamides in the presence of different amines.[a] [a]Reaction conditions: *gem*-difluorohalide ethanes (**1**, **2**, or **7**) : alkynols (**5a** or **5f**) : amines : NaH = 0.48 : 0.57 : 1.44 : 0.96 (mmol) in 3 mL DMSO at 25 °C for 8 h. All the yields refer to the isolated products after column chromatography on silica gel. [b]Yield of the cyclic by-product **24**. [c]Yield of ester **6a′**.

of (2*E*,4*Z*)-dienamide increased linearly, as compared to (2*E*,4*E*)-dienamide, with increasing length of the carbon chain, indicating that steric effects influenced the reaction slightly.[18] In contrast, 2-methylbut-3-yn-2-ol (**5f**) and 4-methylhept-1-yn-3-ol (**5l**) gave the corresponding products (*E*)-**6f** (44%) and (*E*,*Z*)-**6l** (50%) as the sole dienamide, respectively.

The scope of the reaction with respect to amine (R^4R^5NH) was also investigated (Scheme 3). Following the previous results (Table 1, entry 7), the reaction with DMSO in the presence of different amines also gave the corresponding dienamides (*E*)-**12–14** in good yields and high stereoselectivity. Other functionalized amines, such as, 4-amino-1,2,2,6,6-pentamethyl piperidine gave the corresponding dienamide (*E*)-**15**, the core part of antiosteoporotic agent SB 242784,[4a,5a] and morpholine also gave the corresponding dienamide (*E*)-**16** which is a decent replacement of Weinreb amide.[4c,17a] Similarly, aryl compounds **2** and **7** reacted with **5f** in the presence of $MeNH_2$ in DMSO to give (*Z*)-**17** and (*Z*)-**18**, respectively.

To elucidate the feasible reaction mechanism of the dienamide synthesis, several control experiments were performed (ESI† 1.4.). In the first experiment [eqn (i)], the expected intermediate difluoro ynyl ether **19** was obtained in 17% yield within a short reaction time at 0 °C, along with a trace amount of (*E*)-**6b**. Next, *n*-propyl alcohol was reacted with **1** at 0 °C for 1 h. The major product **20** could be explained by a simple S_N2 displacement of the chloride ion by *n*-propyl alcohol, followed by hydrolysis. Subsequently, fluorovinyl ether **21** provides evidence to support the elimination of HF in difluoro ynyl ether **19**. Therefore, we propose the plausible mechanism for the (*E*)-selective 2,4-dienamide synthesis (Scheme 4). First, difluoro propargyl ether (**25**) is formed through an S_N2 displacement of the chloride ion, followed by acidic proton abstraction, yielding the vinyl propargyl ether intermediate **I**.

Subsequently, the sigmatropic rearrangement of intermediate **I** gives allenoyl fluoride **II**, which is trapped by amine to give the corresponding allene amide **III**. To confirm this [3,3]-sigmatropic rearrangement in the reaction, we treated prop-2-en-1-ol (instead of alkynol) with **1** under the same reaction conditions [ESI† 1.4. eqn (ii)]. A mixture of **22**, along with the α,β-unsaturated amide **23** was observed. This experiment indicates that difluoro enyl ether undergoes a [3,3] sigmatropic rearrangement to generate allyl amide **22**, which is further isomerized to **23**.[19] Based on the results of the control experiments [eqn (i and ii)], it was concluded that the subsequent [3,3] sigmatropic rearrangement of an intermediate **I** gave the substituted allenoyl fluoride **II**. After trapping with amine, the obtained allene amide **III** is subsequently enolized to **IV** and further cyclized to pyran intermediate **V**. Finally, a 6π-electrocyclic ring opening reaction[17] leads to the



Scheme 4 Proposed mechanism.

selective formation of 2,4-dienamide (*E*)-**6a** (Scheme 4). The existence of the proposed pyran intermediate **V** and 6π-electrocyclic ring opening in the last step was supported by the last control experiment [ESI† 1.4. eqn (iii)]. When the reaction time for the synthesis of (*E*)-**12** was increased to 24 h, a dihydro pyridinone derivative **24** (22%), along with the desired compound (*E*)-**12** (34%), was formed, indicating that the *in situ* generated reactive allene was trapped by secondary amide,[20] followed by double bond isomerization to generate compound **24**. However, the mixture ((*E*/*Z*)-**6a** and **6a**′) could be generated by the competitive [1,3]-H shift[21] of an acidic α-proton from the allenoyl fluoride **II** leading to amidation or esterification (Scheme 4, highlighted with grey colour). The preferred pathway depends on the substituent at the α, β or δ-position,[22] and isomerization may also have been instigated by an impurity in the reaction medium.[17a]

In summary, we have developed a new synthetic protocol for the direct stereoselective synthesis of functionalized α-substituted 2,4-dienamide *via* three-component reactions of *gem*-difluorochloro ethanes, propargyl alcohols, and amines. The versatility of this method for various substrates can be utilized for the efficient stereoselective synthesis of α-substituted 2,4-dienamide containing molecules.

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Conflicts of interest

The authors declare no conflict of interest.

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