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Synthesis of a stable triformylmethane synthon and its scalable application to 7-acylamino-3-formylquinoline syntheses

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ABSTRACT

Novel 2-iminiomethylvinamidinium trihalides were isolated as stable crystals and found to be useful triformylmethane synthons with non-deliquescent nature in air. They were easier to manufacture, handle, and store than the known 2-iminiomethylvinamidinium dichloride. By virtue of in situ aminal protection, a combination of the vinamidinium salt with a secondary amine achieved an efficient and scalable synthesis of 7-acylamino-3-formylquinoline, a versatile synthetic intermediate for potent anti-obesity drugs 7-acylamino-3-aminomethyl-8-methylquinolines.

1. Introduction

Obesity is a global pandemic.[1] Once considered a problem of high-income countries, obesity is now on the rise in low- and middle-income countries, particularly in urban settings. Existing strategies to combat obesity through lifestyle modification have had limited success and thus new classes of treatments, including pharmacotherapy, are being sought in an attempt to reverse the burden the disease has on all societies. Among the various anti-obesity drugs that have been developed, melanin-concentrating hormone receptor 1 (MCHR1) antagonists have been reported as especially promising agents and the non-peptide compounds **1** were found to be highly potent, orally bioavailable and centrally acting MCHR1 antagonists (Fig. 1).[2]

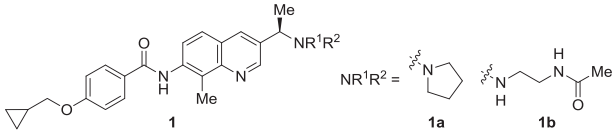
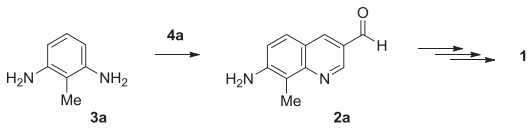
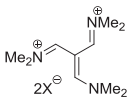


Fig. 1. MCHR1 antagonists **1**.

The potent drugs **1** are characterized by the core chemical structure of 7-acylamino-3-aminomethyl-8-methylquinoline. In their original synthesis, 7-amino-3-formyl-8-methylquinoline **2a** played a major role as a versatile intermediate leading to a series of MCHR1 antagonists (Scheme 1).[2c] The intermediate **2a** was originally synthesized by a quinoline annulation reaction of 2,6-diaminotoluene **3a** with the 2-iminiomethyl substituted vinamidinium (1,5-diazapentadienium) salt **4a** (structure in Fig. 2).



Scheme 1. Original synthesis of MCHR1 antagonists **1**.



4a (X=BF_4), **4b** (X=Cl), **4c** (X=ClO_4), **4d** (X=PF_6)

Fig. 2. Known 2-iminiomethylvinamidinium salts **4**.

Vinamidinium salts[3] are known to be applicable to a variety of aromatic ring annulations, such as substituted quinolines,[4] pyrimidines,[5–7] pyrroles,[8] isoxazoles,[9] pyridines,[10–13] benzenes,[14,15] and fused pyrimidines and pyridines,[16–18] and the

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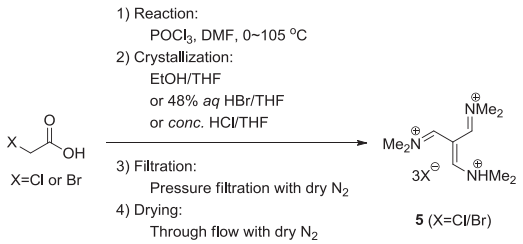
synthetic approach has attracted much attention in not only academia but also industry. As an industrial example, a vinamidinium salt has been used for a pyridine annulation step in the manufacturing process of Etoricoxib.[12] Among the various vinamidinium salts, 2-iminiomethyl substituted vinamidinium salts **4** have become the focus of attention since they can serve as a triformylmethane synthon.[9,19,20] As a synthetic reagent, however, **4** has the commonly noted issue of being hygroscopic. In particular, the Cl salt **4b** is deliquescent leading to decomposition[21] and it is difficult to handle it on large-scale. To overcome the hygroscopicity and deliquescent nature, the ClO_4 salt **4c** was developed and used as an alternative.[5,8] Since a safety assessment revealed that **4c** has high energy content and shock sensitivity,[22,23] the BF_4 salt **4a** has been introduced as an alternative, although it suffers the drawback of showing glass corrosion properties.[4,9] In recent years the non-hygroscopic PF_6 salt **4d** has been discovered and applied for various syntheses.[24] However, **4d** has the drawback of requiring a costly PF_6 anion source.

As part of a drug development program, we recently required access to a scalable and efficient synthesis of the 7-aminosubstituted 3-formylquinoline **2**. Although a variety of quinoline syntheses have been reported, to our knowledge, the only existing synthesis of **2** was the method depicted in Scheme 1.[2b,c,4] Our attention was focused on an application of this methodology, scouting for a novel 2-iminiomethylvinamidinium salt suitable for a large-scale production with the following characteristics: (1) stable in air, (2) non-glass-corrosive, and (3) inexpensive manufacture using common materials. We thought a vinamidinium salt of such nature would become a generally useful tool for aromatic ring annulations. Herein, we report a novel, stable 2-iminiomethylvinamidinium trihalide **5** and its application to an efficient quinoline annulation reaction to provide **2**, a versatile intermediate leading to MCHR1 antagonists **1**.



Scheme 2. Preparation of 2-iminiomethylvinamidinium trihalide **5**.

2. Results and discussion

2.1. Discovery of 2-iminiomethylvinamidinium trihalide

2-Iminiomethylvinamidium salts **4** have been synthesized via Vilsmeier–Haack type reaction using bromoacetic acid with DMF and phosphoryl chloride.[19] The reaction of phosphonoacetic acid,[5] trifluoropropanoic acid,[24] or malonic acid[15] with the Vilsmeier reagent also yielded **4**. Isolation of **4** has been achieved by crystallization from aqueous solution containing a counter anion such as BF_4^-, ClO_4^-, and PF_6^-.[5,15,19,24] For example, in the bromoacetic acid case (reagents ratio used; bromoacetic acid/DMF/phosphoryl chloride=1:15:3),[19] distillation of the remaining DMF and a successive addition of ice and aq $NaBF_4$ gave the desired crystals **4a**.

In our study, the commonly available bromoacetic acid was selected as the starting material and phosphoryl chloride and DMF were used for the in situ preparation of the Vilsmeier reagent (Scheme 2). An excess amount of DMF was used since DMF serves as not only the reagent but also reaction solvent (reagents ratio used; bromoacetic acid/DMF/phosphoryl chloride=1:6:4). We envisioned quenching of the reaction mixture with EtOH instead of water and crystallization of the halide salt by adding anti-solvent THF, which we anticipated would allow crystallization in a non-aqueous solution. In fact, a successive addition of EtOH and THF enabled crystallization directly from the reaction mixture and enabled us to avoid the tedious distillation of the high boiling point DMF. In order to prevent the crystals from absorbing moisture, the subsequent isolation process was carried out by pressure filtration and through-flow drying with dry N_2 (dew point: −80 °C).

Unexpectedly, the ^{1}H NMR spectrum of the isolated crystals showed no peak at around 3.5 ppm in DMSO-d_6 due to water but a singlet peak at around 6.5 ppm, which indicated that the isolated vinamidinium salt was protonated by the acid side product (HCl/HBr). Thus, this procedure provided the unusual vinamidinium trihalide **5** (structure in Scheme 2) instead of the dichloride **4b**. An example of ^{1}H NMR spectra of **5** (X=Cl) is shown in Fig. 3. To our knowledge, 2-iminiomethylvinamidinium salts have only been reported as the salts containing two molecules of counter anions such as **4a**–**d**. We believe this is the first report of a 2-iminiomethylvinamidinium salt, incorporating three molecules of counter anions.

Fortunately, **5** showed better physical properties and was non-deliquescent in air. Consequently, **5** can be easily handled as a synthetic reagent and has a long-shelf-life, only requiring to be kept in an air-tight container at room temperature. In fact, over 3

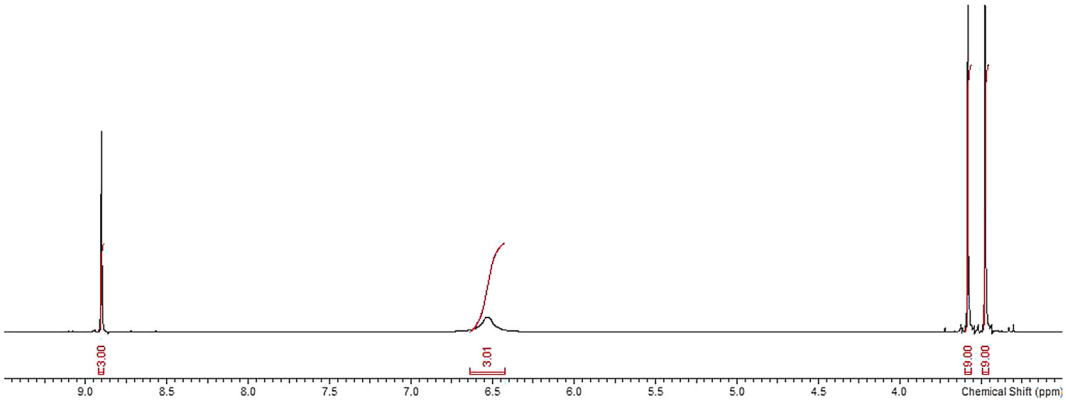


Fig. 3. ^{1}H NMR spectra of **5** (X=Cl).

years have passed since the first synthesis, and ^{1}H NMR demonstrates no significant change in quality. The old lot also showed the same reactivity as the fresh lot in the synthesis of 7-acylamino-3-formyl-8-methylquinoline described later in this report.[25]

In a moisture tolerance assessment of **5** an interesting phenomenon was observed. When the isolated crystals of **5** were placed in a through-flow dryer using air (approximately 50% RH) instead of dry N_2, the ^{1}H NMR spectra of a sample taken in mid-run (9 h) showed a singlet peak due to water at around 3.5 ppm but no peak at around 6.5 ppm. At the end of the run, the crystals were deliquescent and gave a decomposed material, which indicated that moisture in atmosphere gradually replaced 1 mol equiv of the acid (HCl/HBr) to convert **5** to wet **4e** (X=Cl/Br).[26] Fig. 4 shows an example of ^{1}H NMR spectra of **4e** converted from **5** (X=Cl). This result confirmed that dry conditions are necessary for the isolation and storage of **5** in order to prevent the slow but irreversible transformation to **4e**, even though **5** can be easily handled in air.

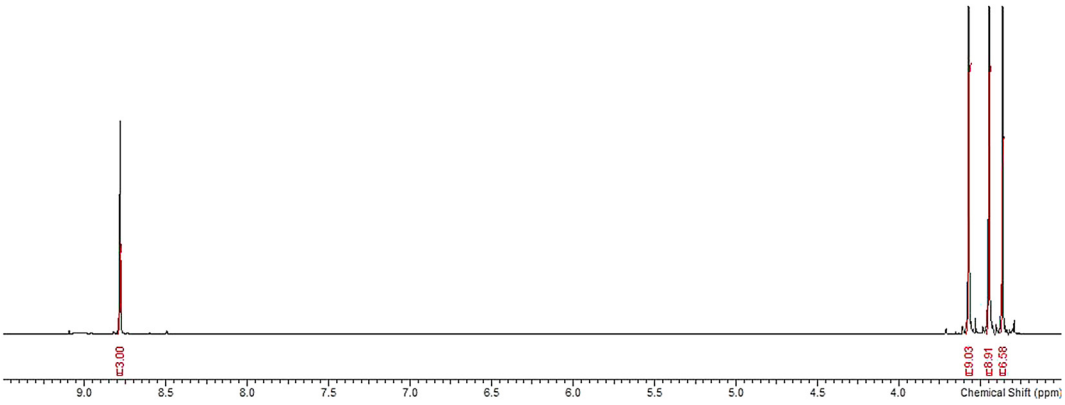


Fig. 4. ^{1}H NMR spectra of **4e** (X=Cl).

2.2. Scalable synthesis of 2-iminiomethylvinamidinium trihalide

With the easy-handling and long-shelf-life vinamidinium salt in hand, our attention was shifted to the development of an industrially feasible manufacturing process for **5**, where three types of issue were addressed. The first issue was how to conduct the extremely exothermic reaction to yield the vinamidinium salt.[21] The 2-chlorovinamidinium salt was obtained at 75 °C,[27] and it was necessary to heat the reaction mixture above 75 °C to get the 2-iminiomethylvinamidinium salt formation to go to completion.[19] In view of the need for careful thermal control of the exothermic multi-step reaction, holding the reaction temperature until completion of the first step transformation was deemed reasonable. A stepwise temperature elevation protocol was adopted as follows: (1) add phosphoryl chloride (4 equiv) to a mixture of α-haloacetic acid (1 equiv) and DMF (6 equiv) at 0 °C, (2) heat the mixture to 80 °C, (3) stir the mixture while keeping the temperature at 80 °C, (4) stir at 95 °C, and (5) stir at 105 °C.

The second issue was how to scale-up the crystallization process. As aforementioned, it was possible to obtain crystals of **5** in non-aqueous EtOH/THF. In fact, reaction following to the stepwise temperature elevation protocol and subsequent crystallization by adding EtOH/THF, furnished a moderate yield (62%) on laboratory scale (Table 1, run 1). However, scale-up experiments resulted in decreased yield (33% in run 2 and 41% in run 3). As batch size was increased it required longer time (up to 3 h) to add EtOH, because of its exothermal behavior, and the extended period may have affected the yield because **5** can react with EtOH to give an acetal species.[20] On the assumption that **5** can be obtained even in the presence of a small amount of water if seed crystals are added when necessary, 48% aq HBr was used for quenching of the reaction mixture instead of EtOH. Fortunately, **5** was obtained as crystals from an aq HBr/THF system, in sharp contrast to EtOH/THF system, giving a moderate yield (69%) even when the addition of aq HBr took 4 h (run 4).

The third issue arose as a consequence of the crystallization solvent change. As a larger portion of water remained in the wet crystals obtained from aq HBr/THF, establishment of an efficient drying procedure became an issue in terms of establishing the manufacturing feasibility. We assessed the scalability of the through-flow drying process and reached the conclusion that a through-flow with warmed dry N_2 gas (approximately 60 °C) would enable a feasible drying process. The established drying

Table 1
Preparation of 2-iminiomethlvinamidinium trihalide **5**

Run	Bromoacetic acid (kg)	Crystallization solvent	**5**		Content of Each contribution (w/w%)				Molar ratio cation/Br/Cl
			kg	Yield[a] (%)	[H_2O][b]	[Br][c]	[Cl][c]	[Cation][d]	
1	0.0227	EtOH/THF	0.0327	62	1.6	26.7	15.0	56.7	1.0:1.1:1.4
2	14.6	EtOH/THF	10.7	33	0.5	19.1	20.2	60.2	1.0:0.7:1.7
3	25.4	EtOH/THF	22.6	41	0.0	16.6	23.1	60.3	1.0:0.6:2.0
4	22.9	48% Aq HBr/THF	37.1	69	5.0	12.5	24.5	58.0	1.0:0.5:2.2
5	49.5	48% Aq HBr/THF	84.1	74	5.3	11.2	25.8	57.6	1.0:0.5:2.3
6	49.5	48% Aq HBr/THF	77.9	71	4.3	13.1	22.6	60.1	1.0:0.5:2.0

[a] Corrected yield based on the vinamidinum cation content.
[b] Water content analyzed by Karl Fisher method.
[c] Br or Cl anion content analyzed by ion chromatography after treatment by oxygen flask combustion method.
[d] Vinamidinium cation content calculated by subtraction method: [Cation]=100−[H_2O]−[Br]−[Cl].

procedure was capable of reducing water content to 5.0% (run 4), and there was no negative impact on stability of the vinamidinium salt.

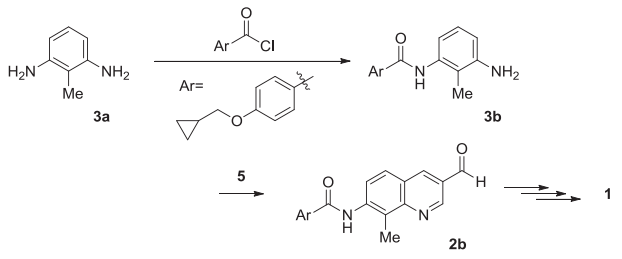
In order to evaluate the scalability and reproducibility of the optimized manufacturing process, two batches of 50 kg were conducted using a procedure with the three aforementioned improvements.[28] As expected, the two batches successfully provided **5** in similar yield (74% for run 5 and 71% for run 6) without any significant issues.

An elemental analysis revealed that the vinamidinium salt **5** contained Br as well as Cl whether or not aq HBr was used as crystallization solvent. For further characterization, the Br free salt was prepared using α-chloroacetic acid and concd HCl instead of α-bromoacetic acid and aq HBr. The isolated crystals were identified as 2-iminiomethylvinamidinium trichloride by the usual analytical methods. As the yield of Br free salt could not be increased above 45%, we continued our studies with the Br containing salt.[29]

The contents of the Br containing salt were determined as follows: as ^{1}H NMR analysis showed that **5** contained a negligible amount of organic impurities, the amount of vinamidinium cation was deductively calculated by a subtraction method with measurable contributions from Br anion, Cl anion, and water. The contents of Br and Cl were determined by ion chromatography after treatment by oxygen flask combustion. The water was assayed by the Karl Fischer method. Table 1 summarizes the analysis data in w/w% and molar ratio of the vinamidinium cation, Br, and Cl. In contrast to crystallization in EtOH/THF, crystallization in aq HBr/THF gave an almost consistent molar ratio of the vinamidinium cation, Br, and Cl (cation/Br/Cl=1.0:0.5:2.0–2.3). To simplify calculation, we treated **5** as a synthetic reagent with the molecular formula of $C_{10}H_{22}N_3Br_{0.5}Cl_{2.5}$ and a molecular weight of 312.89 in our subsequent synthetic studies.

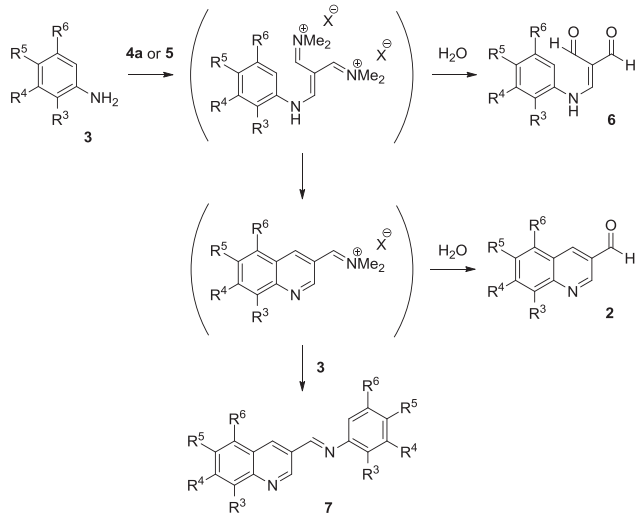
2.3. Synthetic strategy for the MCHR1 antagonists

As depicted in Scheme 1, the original synthesis of **1** began with a quinoline annulation reaction of the diamine **3a** with the vinamidinium BF_4 salt **4a**, to give **2a** in 77% yield.[2b,2c] The downstream transformations, including an amide pendant introduction and an optical resolution, achieved the first synthesis of **1**. In spite of the literature precedents, our preliminary experiments on the quinoline annulation reaction using **3a** resulted in variable yields. To accomplish batch to batch consistency, we introduced a mono *N*-acyl protection to the substrate of the quinoline annulation reaction with **5** (Scheme 3). The choice of **3b** was based on the fact that MCHR1 antagonists **1**, such as **1a** and **1b**, contained the same amide pendant in their structure. With regard to the preparation of **3b**, a selective mono N-acylation approach was used with the symmetrical diamine **3a**. When the reaction was conducted using acyl chloride in toluene/THF (5:3) below 0 °C, the mono *N*-acylated product **3b** was selectively obtained in 92% yield. The selectivity was mostly attributable to the low solubility of **3b**, which precipitated from the reaction mixture and thus remained unreacted in the presence of additional acid chloride.



Scheme 3. Synthetic strategy for MCHR1 antagonists **1**.

Quinoline annulation reaction of 3-substituted, 3,4-disubstituted, and 3,5-disubstituted aniline with vinamidinium salt **4a** was intensively investigated by Tom and co-workers.[4] The reaction was highly sensitive to the electron density of the aniline ring. The reaction of anilines with a methoxy or dimethylamino substituent at the 3-position gave the quinoline **2** in excellent yield (Scheme 4; R^4=OMe, R^3=R^5=R^6=H: 93%; R^4=NMe_2, R^3=R^5=R^6=H: 96%) whereas 3-methyl substituted aniline (R^4=Me, R^3=R^5=R^6=H) resulted in remarkably decreased yield. The reaction at approximately 78 °C in EtOH or AcOH resulted in incomplete cyclization (**2**/**6**=1:2.5) and variable yields (~80–90% as a mixture), and the reaction at approximately 118 °C in *n*-BuOH or AcOH improved the degree of cyclization (**2**/**6**=1:0) but resulted in moderate yield (63%, 71%, respectively). For the 3-Cl substituted aniline (R^4=Cl, R^3=R^5=R^6=H), the degree of cyclization was much lower (AcOH, 118 °C, **2**/**6**=5:12, 72% yield as a mixture).[30] In our case (**3b**; R^3=Me, R^4=NHCOAr, R^5=R^6=H), smooth cyclization was one of the keys to success in our process development.



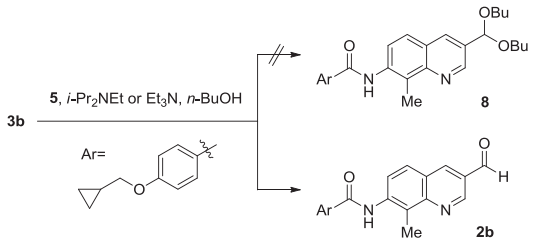
Scheme 4. Quinoline annulation reaction of substituted aniline with 2-iminiomethylvinamidinium salt.

2.4. Scalable synthetic application of 2-iminiomethylvinamidinium trihalide to 7-amino-3-formylquinoline

To develop smooth cyclization conditions, some trials were conducted using two types of solvent. In the first series of trials, AcOH was selected because **5** is highly soluble in AcOH (>20%) unlike common organic solvents including alcohol. Unfortunately, the reaction of **3b** with **5** in AcOH resulted in sluggish and messy reaction giving a number of unknown impurities, including the *N*-acetylated by-product of **3b** and a tarry substance, which caused problems at the isolation stage. The major by-products depended on the reaction temperature. LC–MS analysis suggested that the major by-product after reaction at 70 °C for 19 h was incomplete cyclization by-product **6** and that the major by-product after reaction at 110 °C for 6 h was imine **7**, which gradually increased as the reaction progressed (Scheme 4).

In the second series of trials, the reaction solvent was switched to an alcohol, which enabled a wide range of reaction conditions in terms of pH and additives. High boiling point *n*-BuOH was selected because a high reaction temperature seemed to drive the cyclization, based on the first trials as well as Tom's work.[4] Utilizing the alcohol solvent, we envisioned a potential for acetal protection of the aldehyde moiety as a means to prevent imine generation

(Scheme 5). Considering the stability of the dibutylacetal protection, tertiary amine (*i*-Pr_2NEt or Et_3N) was added in advance to the quinoline annulation reaction, but contrary to our expectations, the reaction directly gave the aldehyde **2b** rather than the dibutylacetal **8**. Meanwhile, using the vinamidinium dihalide **4e** instead of **5** provided the dibutylacetal **8**, which was isolated in 78% yield and then quantitatively converted to **2b** by an acidic hydrolysis. The failure of the acetal protection when using **5** was presumably due to the HCl/HBr salt of the tertiary amine being generated in the reaction mixture.



Scheme 5. Attempts at acetal protection.

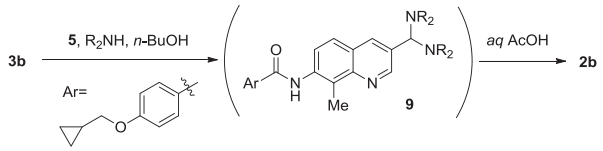
Aside from the unexpected result, the second trials showed that the reaction of **3b** with **5** in *n*-BuOH in the presence of a tertiary amine proceeded much faster and cleaner than did the reaction in AcOH. The reaction at 110 °C was completed in less than 1 h, and the reaction at 80 °C proceeded much cleaner without tarry by-products to completion in 2 h. Owing to the improved reaction profile, **2b** were isolated in 90% yield and 98.4% purity by HPLC analysis. Unfortunately, however, this method showed a significant drawback in that it had a limited tolerance for water. For example, using a vinamidinium salt containing 2.5% of water, the reaction rate obviously decreased and reaction resulted in low conversion (up to 54.6% by HPLC analysis) with a number of by-products, which was significant because the typical water content of **5** was approximately 5% (see Table 1).

In light of the above results, an amendment was made to our strategy for quinoline annulation reaction. We were intrigued by the possibility for in situ aminal protection with a secondary amine instead of acetal protection with alcohol solvent (Table 2). Firstly, a variety of secondary amines, such as *n*-Pr_2NH, *i*-Pr_2NH, piperidine, and morpholine, were screened in the presence of Et_3N in *n*-BuOH at 80 °C (runs 1–4). In all cases, the targeted reaction proceeded well, even with **5** containing approximately 5% water, and the side-reactions to generate **7** as well as the tarry by-product were successfully inhibited. Upon completion of the reaction, we attempted a one-pot hydrolysis followed by crystallization directly from the reaction mixture. Aqueous AcOH was added to the reaction mixture, leading to crystals of the hydrolyzed product **2b** being successfully obtained in good yield (82–86%) and high purity (97.2–99.4% by HPLC analysis) without any other purification. When the amount of **5** was reduced from 2.4 equiv to 1.6 equiv, the sequence of reactions gave a comparable result (run 5). Using 6.0 equiv of morpholine instead of a combination of Et_3N (3.0 equiv) and morpholine (3.0 equiv), the yield was improved to 94% (run 6).

To identify the in situ generated species, some experiments were conducted. When the reaction was carried out at high concentration using morpholine, precipitation occurred in the reaction mixture and the isolated precipitate was identified as morpholine aminal **9a**. Since the isolated yield of **9a** was 91%, the in situ aminal protection was deemed to dominate acetal protection even in alcohol media.

For this secondary amine-based in situ aminal protection system, we assessed the acceptance range of water content that would not have a negative impact on the reaction (Table 3). Firstly, the lower water content of anhydrous **5** was verified to be applicable to this reaction system (run 1), and then a higher water content (11.3% corresponding to the dihydrate of **5**) was examined using **5** with typical water content (5.0%) and additional water (6.3%) (run 3). In this case, the consumption rates of raw material **3b** as well as pre-cyclized intermediate were decreased and it took 24 h for reaction to reach completion. However, the usual work-up, adding aq AcOH, was able to provide **2b** in comparable yield and quality. The study revealed that the in situ aminal protection system had a good tolerance for water content and that **5** containing up to approximately 10% of water could be used in this reaction protocol.

Table 2
Synthesis of **2b** by virtue of in situ aminal protection[a]



Run	**5**[b] (equiv)[c]	Et_3N (equiv)	R_2NH (equiv)	Yield of **2b** (%)	HPLC (area %)
1	2.4	4.5	*n*-Pr_2NH (4.5)	82	97.3
2	2.4	4.5	*i*-Pr_2NH (4.5)	86	97.2
3	2.4	4.5	Piperidine (4.5)	84	98.7
4	2.4	4.5	Morpholine (4.5)	86	99.4
5	1.6	3.0	Morpholine (3.0)	89	99.6
6	1.6	N/A	Morpholine (6.0)	94	99.8

[a] *n*-BuOH, 80 °C 3–8 h.
[b] Water content: 5 w/w%.
[c] Calcd using MW 312.89, not corrected with water content.

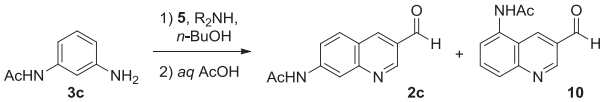
Table 3
Tolerance for water[a]

Run	Water content of **5** (w/w%)	Time (h)	Yield of **2b** (%)	HPLC (area %)
1	0.0	4	88	99.8
2	5.0	3	94	99.8
3	11.3[b]	24	92	99.7

[a] Compound **5** (1.6 equiv, calcd using MW 312.89, not corrected with water contents), morpholine (6.0 equiv), *n*-BuOH, 80 °C.
[b] Sum of water content of **5** (5.0%) and additional water (6.3%).

Finally, the scale-up feasibility of this reaction protocol was assessed by conducting two batches under optimum conditions at 22 kg scale. The first batch using **3b** (21.8 kg) and **5** (37.1 kg, water content: 5.3%) successfully provided **2b** (24.3 kg) in 92% yield with 100.0% purity by HPLC analysis. The successive batch at the same scale also afforded **2b** in 91% yield with 99.9% purity. These results demonstrated that the protocol works at large production scale with good reproducibility.

Furthermore, the applicability of the reaction protocol was evaluated using 3-acetylaminoaniline **3c** as substrate (Scheme 6). Applying a combination of vinamidinium trihalide **5** with a secondary amine, the target product 7-acetylamino-3-formylquinoline **2c** was successfully obtained. Since **3c** has two reactive sites for the cyclization reaction, regioselectivity became a potential issue. In



Scheme 6. Regioselective synthesis of **2c** using the combination of **5** and a secondary amine.

the case of morpholine, regioisomer **10** was generated in 1:13 ratio to **2c** by HPLC analysis and pure **2c** was obtained in 79% yield by a successive one-pot hydrolysis. When the secondary amine was switched to piperidine, regioselectivity was improved to 1:28 and the yield of pure **2c** was also increased to 90%. The result was comparable to that of a reported procedure using the BF_4 salt **4a** (87%).[4]

3. Conclusion

2-Iminiomethylvinamidinium trihalide **5** was isolated as crystals for the first time. A noteworthy feature of **5** is its non-deliquescent nature in air, whereas the dihalide **4b**/**4e** is deliquescent to give a decomposed material. This feature makes it attractive as a synthetic reagent to serve as a triformylmethane synthon. Through intensive scale-up studies, an industrially feasible manufacturing process of **5** has been successfully developed. As a synthetic application of the air stable vinamidinium trihalide, we have also established an efficient and scalable synthesis of the 7-acylamino-3-formy-8-methylquinoline **2b**, a versatile intermediate leading to MCHR1 antagonists **1**. The key to the successful quinoline annulation was an in situ aminal protection of the aldehyde moiety with a secondary amine, which effectively inhibited the problematic side reaction that gave imine **7** and tarry by-product, with good water tolerance. Moreover we demonstrated that the reaction protocol was effective at providing a common substrate **2c**. Another type of synthetic application of **5** is the focus of ongoing research.

4. Experimental section

4.1. General

All materials were purchased from commercial suppliers and used without further purification. Melting points were recorded on a Büchi B-540 micromelting apparatus and were uncorrected. NMR spectra were run at 300 MHz (^{1}H) and 75 MHz (^{13}C) on a Bruker DPX-300 spectrometer. Chemical shifts are reported as δ values using tetramethylsilane as an internal standard and coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, and br=broad. IR spectra were recorded on a Horiba FT-210 spectrophotometer. The mass spectral analyses, microanalyses, and ion chromatography analyses were carried out at Takeda Analytical Research Laboratories, Ltd. HPLC analyses were performed with a Hitachi L-7000. Detection was performed with an ultraviolet absorption photometer (wavelength 254 nm). Purity was determined by HPLC and presented as the area percentage of the compound peak relative to the total area of all the peaks integrated. Water content was determined by Hiranuma AQV-7 Karl Fisher volumetric titrator.

4.2. Synthesis of 2-iminiomethylvinamidinium trichloride (5, as Br free salt)

To a solution of 2-chloroacetic acid (2.00 g, 21.2 mmol) in DMF (18.6 g, 254 mmol) was added dropwise phosphoryl chloride (26.0 g, 170 mmol) at 0 °C. The mixture was stirred at 80 °C for 1 h, at 95 °C for 1 h, and at 105 °C for 1 h. After concd HCl (4.29 g, 42.4 mmol) and THF (120 mL) were successively added at room temperature, the mixture was stirred for 0.5 h. The resultant precipitate was collected by dry N_2 pressure filtration, washed with THF (40 mL), and dried by through-flow drying to give **5** (5.10 g, 16.5 mmol, 78% yield, as monohydrate) as white crystals. Mp 129–131 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.48 (s, 9H), 3.59 (s, 9H), 6.95 (br s, 3H), 8.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.78, 48.80, 91.43, 165.24; IR (ATR) ν 1619, 1453, 1417, 1319 cm^{-1}. Anal. Calcd for $C_{10}H_{22}N_3Cl_3\cdot H_2O$: C, 38.91; H, 7.84; N, 13.61; Cl, 34.36. Found: C, 38.56; H, 8.21; N, 13.63; Cl, 34.58.

4.3. Synthesis of 2-iminiomethylvinamidinium trihalide (5, as Br containing salt)

To a solution of 2-bromoacetic acid (49.5 kg, 356 mol) in DMF (155.7 kg, 2130 mol) was added dropwise phosphoryl chloride (217.9 kg, 1421 mol) at 0 °C. The mixture was stirred at 80 °C for 1 h, at 95 °C for 1 h and at 105 °C for 1 h. 48% Aqueous HBr (119.7 kg, 710 mol) and THF (877 kg) were successively added dropwise to the mixture. After stirring for 2 h, the resultant precipitate was collected by dry N_2 pressure filtration, washed with THF (439 kg)/EtOH (78 kg), and dried by through-flow drying with warmed dry N_2 at 60 °C to give **5** (84.1 kg, 263 mol, 74% yield, H_2O: 5.3 w/w%) as white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.48 (s, 9H), 3.59 (s, 9H), 6.86 (br s, 3H), 8.87 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.77, 48.88, 91.45, 165.24.

4.4. Conversion of 5 to 2-iminiomethylvinamidinium dihalide (4e)

2-Iminiomethylvinamidinium trihalide **5** (50.0 g) was humidified by through-flow with air (approximately 50% RH) at room temperature for 9 h to give **4e** (45.9 g) as a brown solid.[26] ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.48 (s, 9H), 3.59 (s, 9H), 3.65 (br s, 2H), 8.91 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.81, 48.86, 91.44, 165.20.

4.5. Synthesis of *N*-(3-amino-2-methylphenyl)-4-(cyclopropylmethoxy)benzamide (3b)

To a solution of ethyl 4-hydroxybenzoate (24.6 kg, 148 mol) in 20% NaOEt/EtOH (55.3 kg, 163 mol) was added (bromomethyl)cyclopropane (30 kg, 222 mol). The mixture was refluxed 3 h and then refluxed with 3 N aq NaOH (73.9 kg, 222 mol) for 2 h. After acidified with concd HCl (59 kg), the mixture was cooled to room temperature. The resultant precipitate was collected by filtration, washed with water/EtOH (2:1, 46 kg), and dried in vacuo to give 4-(cyclopropylmethoxy)-benzoic acid (26.6 kg, 138 mol, 93% yield) as white crystals. Mp 180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.35–0.40 (m, 2H), 0.64–0.70 (m, 2H), 1.27–1.31 (m, 1H), 3.88 (d, J=6.9 Hz, 2H), 6.91–6.96 (m, 2H), 8.03–8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.23, 10.08, 72.96, 114.27, 121.48, 132.34, 163.54, 171.67; IR (KBr) ν 3084, 1675 cm^{-1}; MS (FAB) m/z 193 $(MH)^+$. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.48; H, 6.20.

To a suspension of 4-(cyclopropylmethoxy)benzoic acid (25.0 kg, 130 mol) in toluene (217 kg) were added DMF (0.5 kg) and thionyl chloride (18.6 kg, 156 mol). The mixture was stirred at 40–50 °C for 1 h. The acid chloride solution was added to a suspension of 2,6-diaminotoluene (**3a**, 23.8 kg, 195 mol) and TEA (35.5 kg, 351 mol) in toluene/THF (5:3, 350 kg) below 0 °C. The mixture was stirred at the same temperature for 0.5 h and then at room temperature for 2 h. After adding acetone (791 kg) and water (200 kg), the layers were separated. The separated organic layer was washed with 5% aq $NaHCO_3$ (205 kg) and water (200 kg) and then the solvent was switched to EtOH (198 kg) via vacuum concentration. After stirring the slurry at room temperature for 1 h, the resultant precipitate was collected by filtration, washed with EtOH (237 kg), and dried in vacuo to give **3b** (35.4 kg, 119 mol, 92% yield) as white crystals. Mp 202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.33–0.37 (m, 2H), 0.56–0.62 (m, 2H), 1.21–1.27 (m, 1H), 1.91 (s, 3H), 3.89 (d, J=6.9 Hz, 2H), 4.86 (s, 2H), 6.49–6.57 (m, 2H), 6.86–6.93 (m, 1H), 6.96–7.07 (m, 2H), 7.89–7.99 (m, 2H), 9.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.98, 10.93, 13.05, 73.12, 112.94, 114.87, 116.04, 118.90, 126.30, 127.58, 130.28, 137.68, 148.10, 161.97, 165.55; IR (KBr) ν 3419, 3313, 1644 cm^{-1}; MS (FAB) m/z 297 $(MH)^+$.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.90; H, 6.82; N, 9.59.

4.6. Synthesis of 4-cyclopropylmethoxy-*N*-(3-dibutoxymethyl-8-methylquinolin-7-yl)benzamide (8)

To a slurry of **4e** (8.60 g) in *n*-BuOH (100 mL) was added **3b** (5.00 g, 16.9 mmol). The mixture was stirred at 110 °C for 65 h and then concentrated in vacuo. The residue (21.8 g) was dissolved in MeCN (25 mL) and then water (25 mL) was added to the solution at room temperature. The resultant precipitate was collected by filtration, washed with 50% aq MeCN (50 mL), and dried in vacuo to give **8** (6.49 g, 13.2 mmol, 78% yield) as white crystals. Mp 125–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42–0.37 (m, 2H), 0.72–0.66 (m, 2H), 0.93 (t, J=7.3 Hz, 6H), 1.33–1.28 (m, 1H), 1.49–1.37 (m, 4H), 1.68–1.59 (m, 4H), 2.81 (s, 3H), 3.63–3.50 (m, 4H), 3.89 (d, J=6.9 Hz, 2H), 5.75 (s, 1H), 7.00 (d, J=8.8 Hz, 2H), 7.74 (d, J=8.9 Hz, 1H), 7.94–7.90 (m, 3H), 8.19 (d, J=1.8 Hz, 1H), 8.29 (d, J=8.9 Hz, 1H), 9.00 (d, J=2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.66, 10.53, 11.84, 14.29, 19.88, 32.23, 65.67, 73.41, 100.29, 115.08, 123.42, 125.55, 125.91, 126.59, 127.20, 129.42, 131.26, 134.49, 137.14, 147.54, 149.35, 162.59, 165.65; IR (KBr) ν 1647, 1609, 1507, 1256 cm^{-1}; MS (ESI) m/z 491 $(MH)^+$. Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.35; H, 7.85; N, 5.65.

4.7. Hydrolysis of 8

To a slurry of **8** (5.00 g, 10.2 mmol) in MeCN (25 mL) was added 6 N HCl (2.5 mL, 15.0 mmol) at 50 °C. After cooling to room temperature, water (20 mL) and 5 N aq NaOH (3.0 mL, 15.0 mmol) were added to the mixture. After stirring at room temperature for 1.5 h, the resultant precipitate was collected by filtration, washed with 50% aq MeCN (10 mL), and dried in vacuo to give **2b** (3.57 g, 9.91 mmol, 97% yield) as white crystals.

4.8. Synthesis of 4-cyclopropylmethoxy-*N*-[3-(di-morpholin-4-yl-methyl)-8-methylquinolin-7-yl]benzamide (9a)

To a slurry of **5** (859 mg, 2.75 mmol) in *n*-BuOH (5 mL) were added morpholine (884 mg, 10.2 mmol) and **3b** (500 mg, 1.69 mmol). The mixture was stirred at 80 °C for 3 h and then stirred at room temperature for 1.5 h. The resultant precipitate was collected by filtration, washed with *n*-BuOH (10 mL), and dried in vacuo to give **9a** (796 mg, 1.54 mmol, 91% yield) as white crystals. Mp 206–208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42–0.37 (m, 2H), 0.72–0.66 (m, 2H), 1.34–1.29 (m, 1H), 2.56–2.43 (m, 8H), 2.82 (s, 3H), 3.70 (t, J=4.5 Hz, 8H), 3.91–3.88 (m, 3H), 7.01 (d, J=8.8 Hz, 2H), 7.73 (d, J=8.9 Hz, 1H), 7.96–7.89 (m, 4H), 8.32 (d, J=8.9 Hz, 1H), 8.86 (d, J=2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.66, 10.53, 11.76, 50.00, 67.48, 73.42, 87.68, 115.08, 123.62, 125.55, 125.90, 126.25, 126.51, 127.16, 129.45, 136.32, 137.13, 147.54, 150.58, 162.61, 165.66; IR (KBr) ν 1652, 1638, 1609, 1108 cm^{-1}. Anal. Calcd for $C_{30}H_{36}N_4O_4$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.82; H, 7.06; N, 10.88.

4.9. Synthesis of 4-cyclopropylmethoxy-*N*-(3-formyl-8-methyl-quinolin-7-yl)benzamide (2b) via in situ aminal protection

To a slurry of **5** (37.0 kg, 118 mol) in *n*-BuOH (264 kg) were added morpholine (38.7 kg, 442 mol) and **3b** (21.8 kg, 73.6 mol). The mixture was stirred at 80 °C for 4 h. AcOH (57 kg) and water (54 kg) were successively added to the mixture at the same temperature. After cooling to room temperature, the mixture was stirred for 1 h. The resultant precipitate was collected by filtration, washed with 90% aq AcOH (60 kg)/water (48 kg) and water (109 kg). The wet crystals were dried in vacuo to give **2b** (24.3 kg, 67.4 mol, 92% yield) as white crystals. Mp 201–202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.39–0.34 (m, 2H), 0.63–0.57 (m, 2H), 1.29–1.24 (m, 1H), 2.69 (s, 3H), 3.93 (d, J=7.0 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H), 7.82 (d, J=8.7 Hz, 1H), 8.07–8.01 (m, 3H), 8.92 (d, J=2.0 Hz, 1H), 9.31 (d, J=2.0 Hz, 1H), 10.14 (s, 1H), 10.26 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 4.00, 10.91, 13.42, 73.21, 115.05, 125.54, 126.91, 127.82, 128.00, 128.66, 130.64, 131.38, 140.90, 141.08, 148.90, 150.06, 162.42, 165.76,193.11; IR (KBr) ν 1695, 1606, 1503, 1285, 1250 cm^{-1}; MS (ESI) m/z 361 $(MH)^+$. Anal. Calcd for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.53; H, 5.66; N, 7.78.

4.10. Synthesis of *N*-(3-formylquinolin-7-yl)acetamide (2c)

To a slurry of **5** (1.53 g, 4.89 mmol) in *n*-BuOH (10 mL) were added piperidine (1.28 g, 15.03 mmol) and **3c** (0.50 g, 3.33 mmol). The mixture was stirred at 80 °C for 2 h. After AcOH (5 mL) and water (5 mL) were added, the mixture was concentrated in vacuo. The remaining mixture was dissolved in water (10 mL). After 5 N NaOH aq solution (5 mL) was added, the mixture was stirred at room temperature for 1 h. The resultant precipitate was collected by filtration, washed with water (10 mL), and dried in vacuo to give **2c** (0.64 g, 2.99 mmol, 90% yield) as pale yellow crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.16 (s, 3H), 7.81 (dd, J=2.0, 8.9 Hz, 1H), 8.13 (d, J=8.9 Hz, 1H), 8.51 (d, J=1.7 Hz, 1H), 8.83 (d, J=2.0 Hz, 1H), 9.21 (d, J=2.0 Hz, 1H), 10.18 (s, 1H), 10.50 (s, 1H); MS (ESI) m/z 215 $(MH)^+$. Anal. Calcd for $C_{12}H_{10}N_2O_2 \cdot 1H_2O$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.05; H, 5.11; N, 12.02.

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References and notes

1. The current situation of obesity, see' (a) Kim, G. W.; Lin, J. E.; Blomain, E. S.; Waldman, S. A. *Expert Opin. Drug Discov.* **2013**, *8*, 655–671; (b) Obesity and Overweight; Fact Sheet No. 311. World Health Organization: Geneva, Switzerland. http://www.who.int/mediacentre/factsheets/fs311/en/index.html.
2. Many articles and reviews were reported, including: (a) Takekawa, S.; Asami, A.; Ishihara, Y.; Terauchi, J.; Kato, K.; Shimomura, Y.; Mori, M.; Murakoshi, H.; Kato, K.; Suzuki, N.; Nishimura, O.; Fujino, M. *Eur. J. Pharmacol.* **2002**, *438*, 129–135; (b) Kamata, M.; Yamashita, T.; Imaeda, T.; Tanaka, T.; Masada, S.; Kamaura, M.; Kasai, S.; Hara, R.; Sasaki, S.; Takekawa, S.; Asami, A.; Kaisho, T.; Suzuki, N.; Ashina, S.; Ogino, H.; Nakano, Y.; Nagisa, Y.; Kato, K.; Kato, K.; Ishihara, Y. *J. Med. Chem.* **2012**, *55*, 2353–2366; (c) Kasai, S.; Kamata, M.; Masada, S.; Kunitomo, J.; Kamaura, M.; Okawa, T.; Takami, K.; Ogino, H.; Nakano, Y.; Ashina, S.; Watanabe, K.; Kaisho, T.; Imai, Y. N.; Ryu, S.; Nakayama, M.; Nagisa, Y.; Takekawa, S.; Kato, K.; Murata, T.; Suzuki, N.; Ishihara, Y. *J. Med. Chem.* **2012**, *55*, 4336–4351.
3. Lloyd, D.; Mcnab, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 459–468.
4. Tom, N. J.; Ruel, E. M. *Synthesis* **2001**, 1351–1355.
5. Gupton, J. T.; Gall, J. E.; Riesinger, S. W.; Smith, S. Q.; Bevirt, K. M. *J. Heterocycl. Chem.* **1991**, *28*, 1281–1285.
6. Keen, S. P.; Cowden, C. J.; Bishop, B. C.; Brands, K. M. J.; Davies, A. J.; Dolling, U. H.; Lieberman, D. R.; Stewart, G. W. *J. Org. Chem.* **2005**, *70*, 1771–1779.
7. Adnen, H. A. M.; Jameleddine, K.; Bechir, B. H. *Mol. Divers.* **2008**, *12*, 61–64.
8. Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W. *J. Org. Chem.* **1990**, *55*, 4735–4740.
9. Angus, R. O., Jr.; Bryce, M. R.; Keshavarz-K, M.; Wudl, F. *Synthesis* **1988**, 746–748.
10. Petrich, S. A.; Hicks, F. A.; Wilkinson, D. R.; Tarrant, J. G.; Bruno, S. M.; Vargas, M.; Hosein, K. N.; Gupton, J. T. *Tetrahedron* **1995**, *51*, 1575–1584.
11. Marcoux, J.-F.; Corley, E. G.; Rossen, K.; Pye, P.; Wu, J.; Robbins, M. A.; Davies, I. W.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2339–2341.
12. Davies, I. W.; Marcoux, J.-F.; Corley, E. G.; Journet, M.; Cai, D.-W.; Palucki, M.; Wu, J.; Larsen, R. D.; Rossen, K.; Pye, P. J.; DiMichele, L.; Dormer, P.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 8415–8420.
13. Marcoux, J.-F.; Marcotte, F.-A.; Wu, J.; Dormer, P. G.; Davies, I. W.; Hughes, D.; Reider, P. J. *J. Org. Chem.* **2001**, *66*, 4194–4199.
14. Davies, I. W.; Marcoux, J.-F.; Kuethe, J. T.; Lankshear, M. D.; Taylor, J. D. O.; Tsou, N.; Dormer, P. G.; Hughes, D. L. *J. Org. Chem.* **2004**, *69*, 1298–1308.

15. Jameleddine, K.; Adnen, H. A. M.; Béchir, B. H. *Tetrahedron Lett.* **2006**, *47*, 2973–2975.
16. Mityuk, A. P.; Kolodych, S. E.; Mytnyk, S. A.; Dmytriv, Y. V.; Volochnyuk, D. M.; Mykhailiuk, P. K.; Tolmachev, A. A. *Synthesis* **2010**, 2767–2770.
17. Samar, C.; Fayçel, J.; Jameleddine, K. *Tetrahedron Lett.* **2011**, *52*, 3648–3650.
18. Ayed, M. A. H.; Gmiza, T.; Khiari, J. E.; Hassine, B. B. *Synth. Commun.* **2012**, *42*, 1824–1831.
19. Keshavartz-, K. M.; Cox, S. D.; Angus, R. O., Jr.; Wudl, F. *Synthesis* **1988**, 641–644.
20. Budesinsky, M.; Fiedler, P.; Arnold, Z. *Synthesis* **1989**, *11*, 858–860.
21. Davies, I. W.; Marcoux, J.-F.; Wu, J.; Palucki, M.; Corley, E. G.; Robbins, M. A.; Tsou, N.; Ball, R. G.; Dormer, P.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 4571–4574.
22. Ragan, J. A.; McDermott, R. E.; Jones, B. P.; am Ende, D. J.; Clifford, P. J.; McHardy, S. J.; Heck, S. D.; Liras, S.; Segelstein, B. E. *Synlett* **2000**, 1172–1174.
23. Ragan, J. A.; am Ende, D. J.; McHardy, S. J.; Liras, S. *Chem. Eng. News* **2000**, *78*, 8.
24. Davies, I. W.; Tellers, D. M.; Shultz, C. S.; Fleitz, F. J.; Cai, D.; Sun, Y. *Org. Lett.* **2002**, *4*, 2969–2972.
25. With the old lot of **5**, **2b** was obtained in 95% yield with 99.3 % purity by HPLC peak area analysis.
26. An elemental analysis of **4e** was unavailable due to its deliquescent nature. There seemed to be a possibility that **4b** also contained Br counter anion.
27. Palucki, M.; Lin, Z.; Sun, Y. *Org. Process Res. Dev.* **2005**, *9*, 141–148.
28. Comprehensive safety evaluations should be conducted before further attempts to scale-up.
29. As the process research progressed, the yield of Br free salt was improved to 78% by using the doubled amount of DMF and phosphoryl chloride. The procedure is in Experimental section.
30. In this case, regioselectivity in cyclization step was also problematic.