# An Interrupted Schmidt Reaction: C−C Bond Formation Arising from Nitrilium Ion Capture

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ABSTRACT: The rerouting of the nitrilium ion formed in the Schmidt reaction of ketones and TMSN$_3$ to encompass C−C bond formation with an electron-rich aromatic group is reported. Thus, when the reaction is carried out in HFIP using AlCl$_3$ or AlBr$_3$ as the promoter, imines, iminium ions, or enamide derivatives are obtained through one-pot procedures. The scope and possible mechanisms of these new transformations are considered.
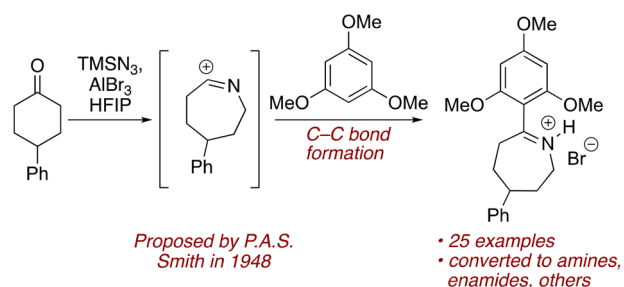
In its original and best-known form, the Schmidt reaction is the acid-mediated conversion of a ketone to an amide using hydrazoic acid or its equivalent.[1] The most commonly accepted mechanism of the reaction, as proposed by P. A. S. Smith in 1948,[2] involves addition of the azide component to the carbonyl followed by dehydration to afford a diazoiminium ion intermediate, which in turn undergoes loss of N$_2$ along with migration of an alkyl group to afford a key nitrilium ion intermediate (Scheme 1). The "normal" Schmidt product is

Scheme 1. Generation and Trapping of Nitrilium Ions through Schmidt Chemistry
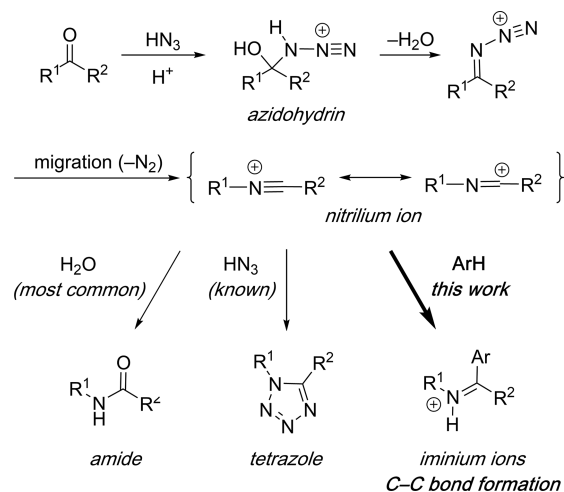
the amide obtained from the addition of water to the nitrilium ion. As reported by K. F. Schmidt in the very first disclosure of this chemistry,[3] these reactions may also afford a tetrazole product under some conditions (e.g., at high concentrations of azide). In the intervening decades, very few examples of

Table 1. Survey of Reaction Conditions[a]
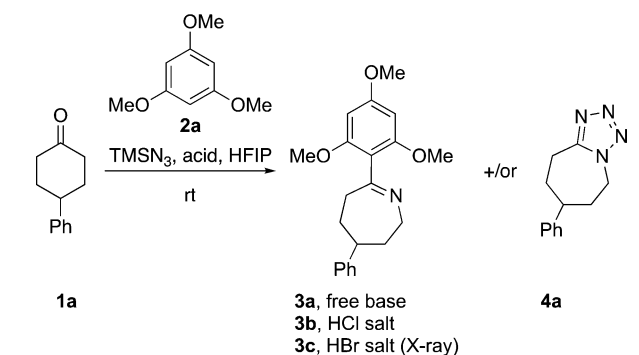
entry	conditions[b]	products (% conv.[c]); yield (%)[d]
1	BF$_3$·OEt$_2$	**1a** (47) + **3a** (46) + **4a** (4)
2	TiCl$_4$	**3a** (68)
3	TfOH	**1a** (17) + **3a** (60) + **4a** (7)
4	Al(OTf)$_3$	**1a** (46) + **3a** (38) + **4a** (10)
5	AlCl$_3$	**3a** (74); 54%
6	AlCl$_3$ (2 equiv)	**3a** (88); 75%
7	AlCl$_3$ (no basic workup)	**3b** (83); 78%
8	AlBr$_3$	**3a** (95); 83%
9	AlBr$_3$ (no basic workup)	**3c** (>100); 92%[e]
10	AlCl$_3$ (no slow addition)	**1a** (20) + **3a** (54) + **4a** (23)
11	AlBr$_3$ (1:2 TFE/HFIP as the solvent)	**1a** (21) + **3a** (42)
12	AlCl$_3$ (1:2 toluene/HFIP as the solvent)	**1a** (90) + **3a** (10)

[a]Results of representative experiments are presented; see Tables S1 and S2 for full results. [b]See the SI for detailed procedures; 1 equiv of acid and NaHCO$_3$ workup unless otherwise noted. [c]% conversion as determined by NMR analysis. [d]Isolated yields. [e]A single preparation of this example was carried out on a 1.2 mmol scale; an 80% yield was obtained in that reaction.
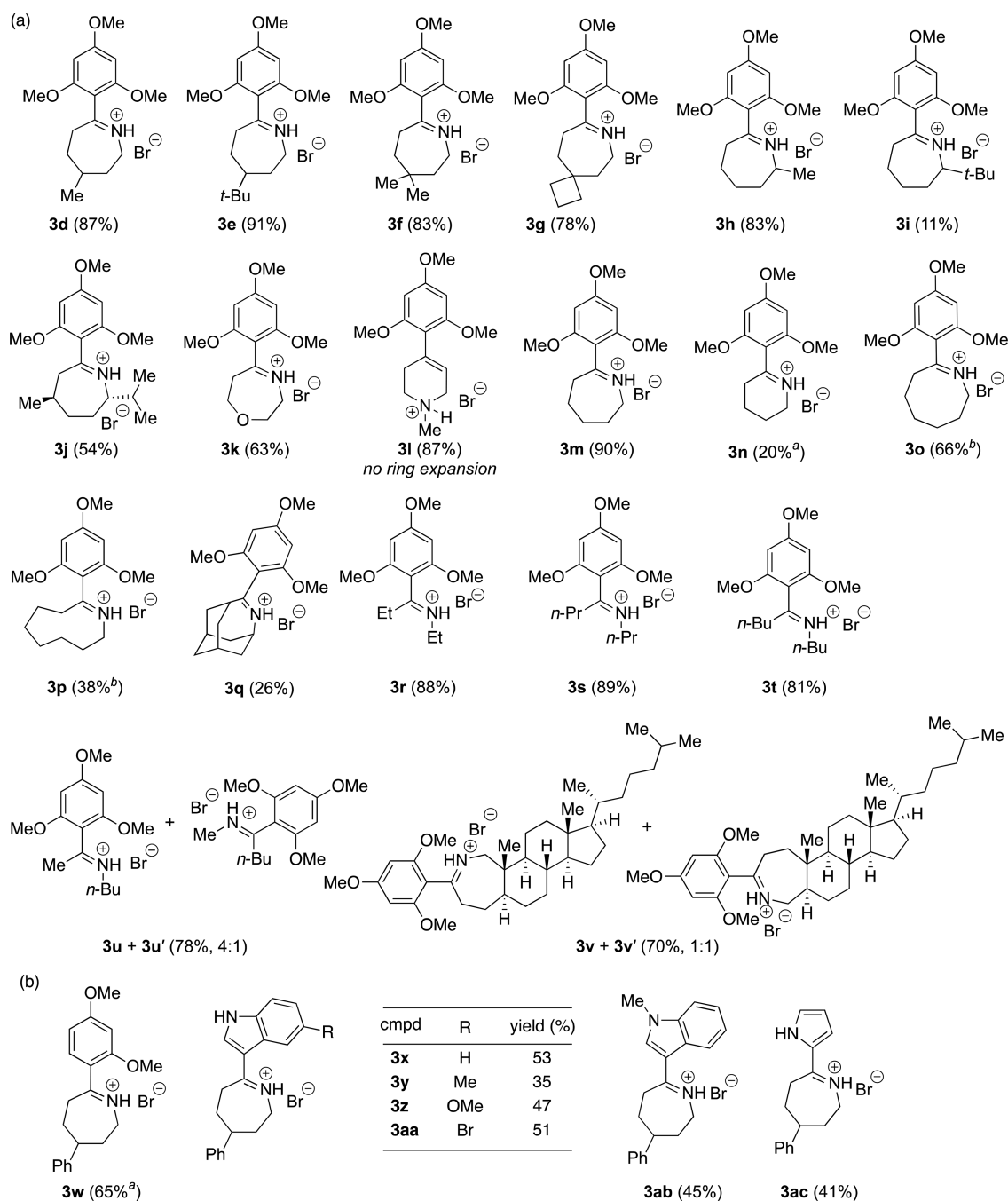
Figure 1. Studies of the reaction scopes of (a) ketones and (b) nucleophiles. The reactions were carried out as described in Table 1, entry 9; see the SI for reaction details. Isolated yields are shown, unless otherwise noted. Notes: [a]NMR yield. [b]Accompanied by a 2−19% yield of the corresponding tetrazole.
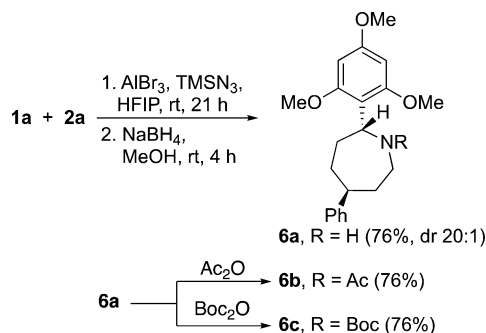
intercepting the nitrilium ion with other oxygen or nitrogen—but not carbon—nucleophiles have been noted.[4] In contrast, similar intermediates obtained through the Beckmann rearrangement of oximes are known to react with allylsilanes,[5] organometallics,[6] and other reagents.[7] Such "interrupted" reactions, a class that also includes Nazarov,[8] Pummerer,[9] Fischer,[10] and Bischler−Napieralski[11] variations, enhance synthetic efficiency by combining multiple bond formations in a single step.

We recently examined the Schmidt reaction of ketones with trimethylsilyl azide to investigate the effect of the highly hydrogen-bonding solvent hexafluoroisopropanol (HFIP) on the reaction.[4c] In that work, we found that the main product of the reaction carried out in HFIP was the tetrazole rather than

the lactam, with little dependence on the stoichiometry. These results suggest that if an azide nucleophile more efficiently reacts with a nitrilium ion in HFIP relative to other solvents, other nucleophiles may do so as well, thus opening the door to an interrupted Schmidt reaction accompanied by C−C bond formation at the position of the nitrilium ion. Here we describe the successful realization of this concept and its application to the synthesis of imines, iminium ions, and enamides, all of which are staples in preparative nitrogen chemistry.

We first sought appropriate mediators for the reaction of 4-phenylcyclohexanone (**1a**) with trimethylsilyl azide and 1,3,5-trimethoxybenzene (**2a**) in HFIP. The most promising results obtained from screening of 22 acids are shown

Scheme 2. Direct Reduction of Iminium Species

6a, R = H (76%, dr 20:1)

6b, R = Ac (76%)

6c, R = Boc (76%)

Scheme 3. One-Pot Conversion of Ketones to Enamides and Related Compounds

Ketones **1**

Compounds **3**
Not isolated

(a) Products from E$^+$ = RC(O)Cl

7a (82%)

7b (86%)

7c (61%)

7d (81%)

7e (59%)

7f (81%)

(b) From RSO$_2$Cl

7g, X = NO$_2$ (70%)
7h, X = Br (75%)
7i, X = OMe (37%)

8a, R = Me (75%)
8b, R = p-tolyl (58%)
8c, R = p-NO$_2$C$_6$H$_4$ (29%)

(c) From isocyanate or Boc$_2$O

9a, X = N-p-C$_6$H$_4$Cl (51%)
9b, X = N-p-C$_6$H$_4$CO$_2$Me (49%)
**9c**, X = O-t-Bu (77%)

in Table 1 (the full list is provided in Tables S1 and S2 in the Supporting Information (SI)). These attempts clearly demonstrate that the nitrilium ion presumably formed under these conditions can lead to C−C bond formation, with particularly good results obtained using AlCl$_3$ and AlBr$_3$ (Table 1, entries 5 and 8). Optimization experiments led us to identify slow addition and 1 equiv of AlBr$_3$ (as opposed to 2 equiv of AlCl$_3$) for these experiments (see Tables S3 and S4 for details). The reactions afforded iminium ions **3b** and **3c**, respectively, as the primary products, which could be isolated or converted to free base **3a** with a basic workup (cf. entries 5 and 7 and entries 8 and 9). An X-ray structure of compound **3c** was obtained (CCDC 1832152; also see the SI). We presume that the salts arise from the reaction of the AlX$_3$ promoter with HFIP solvent to provide a source of HX. Diluting HFIP with either trifluoroethanol or toluene greatly diminished the reaction conversion, as did omitting the slow addition of azide (entries 11 and 12). Under some conditions, tetrazole product **4a** was noted as a minor byproduct, but the typical Schmidt product, 5-phenylcaprolactam (**5a**), was rarely observed (Tables S1 and S2).

With AlBr$_3$ as the promoter, a range of cyclic and acyclic substrates were successfully reacted to afford iminium salts following nonbasic workup (Figure 1a). Reactions were performed with slow addition of TMSN$_3$ and stirring overnight (some reactions also benefitted from heating to 35 °C; conditions for specific compounds are available in the SI). In general, the reaction was most useful for five- to seven-membered cyclic ketones, although highly hindered examples and smaller-ring ketones, many of which are known to be problematic in Schmidt chemistry,[1,12] gave poorer results. Among the heterocyclic ketones tested, tetrahydropyran-4-one gave **3k** in 63% yield, whereas basic 1-methylpiperidine-4-one did not afford the corresponding imine. Instead, the ketone reacted with 1,3,5-trimethoxybenzene via an addition−elimination reaction to afford **3l**. Attempted reactions on two aromatic substrates, flavanone and α-tetralone, led to quantitative recovery of the starting ketones. Acyclic ketones also provided good conversions, affording **3r−u**. Unsurprisingly, the unsymmetrical substrate 2-hexanone gave a mixture of constitutional isomers (**3u** + **3u′**), as did the steroidal substrate 5α-cholestane (**3v** + **3v′**).

In contrast to the wide scope of ketone reactants, the reaction is currently limited to highly electron-rich aromatic nucleophiles (Figure 1b). In addition to 1,3,5-trimethoxybenzene, we were able to achieve good conversions using 1,3-dimethoxybenzene, pyrrole, and a number of substituted indoles. Unsuccessful nucleophiles attempted under the present protocol include 1,2,3-trimethoxybenzene, anisole, benzothiophene, furan, and allyltrimethylsilane. Here we report 25 successful examples of this reaction.
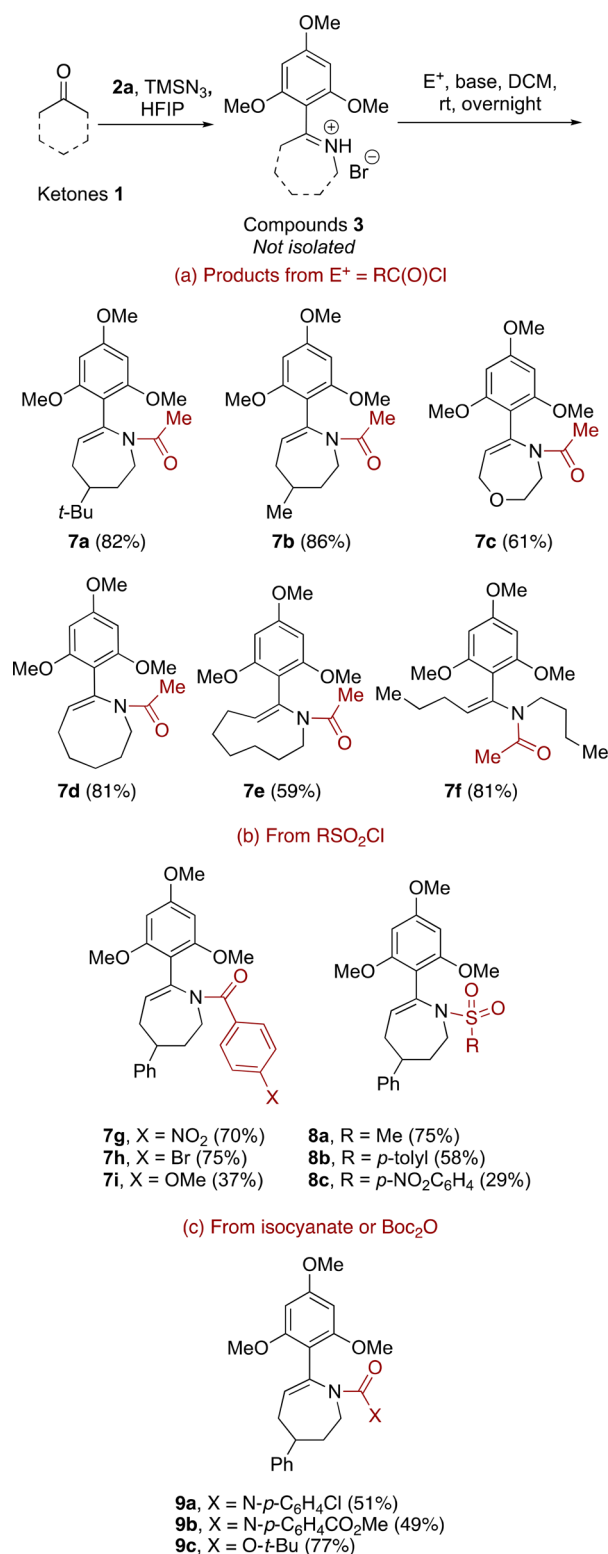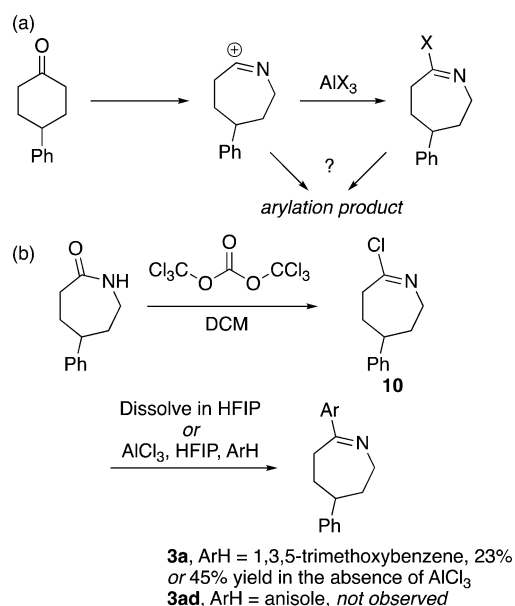
The iminium ions formed in this process are versatile synthetic intermediates. For example, the iminium ion obtained from the reaction of **1a** with **2a** is readily and stereoselectively reduced with NaBH$_4$ to afford **6a** without isolation or purification of the imine intermediate (Scheme 2).

This ring-expansion/arylation sequence was readily extrapolated to enable an unprecedented one-pot conversion of

ketones to ring-expanded enamide derivatives (Scheme 3). Enamides are useful synthetic intermediates with application to natural product chemistry that warrant expanded synthetic access.[13] Thus, iminium ion **3c** was generated from ketone **1a** by treatment with TMSN$_3$ under AlBr$_3$ promotion and subsequently reacted with a series of electrophiles to afford enamide, sulfonamide, or urea derivatives.

Our initial hypothesis rested on the idea that the nitrilium ion was more persistent or more reactive in HFIP compared with other solvents. We have now reconsidered this, especially given the narrow scope of Lewis acids that can promote this kind of interrupted Schmidt reaction. In particular, the success of AlCl$_3$ and especially AlBr$_3$ suggests that these reagents, which are used in stoichiometric amounts, may intercept the nitrilium ion to generate an iminyl chloride or bromide. Either the nitrilium ion or the iminyl halide could in principle react with the nucleophilic aromatic reaction partner (Scheme 4a).

Scheme 4. Mechanistic Possibilities

3a, ArH = 1,3,5-trimethoxybenzene, 23% or 45% yield in the absence of AlCl$_3$
3ad, ArH = anisole, *not observed*

The iminium ion could also react, possibly reversibly, with HFIP solvent (where X in Scheme 4 would be O(CF$_3$)$_2$), although this was not observed and may be considered unlikely given the low nucleophilicity of this solvent.

The allowable intermediacy of the iminyl halide was demonstrated by preparing a solution of iminyl chloride **10** from 4-phenylcaprolactam and triphosgene.[14] A 23% yield of the arylation product was obtained when 1,3,5-trimethoxybenzene was added along with AlCl$_3$, showing that the iminyl chloride can react in this Friedel–Crafts (FC) process (Scheme 4b). Interestingly, a higher yield of coupled product was obtained when AlCl$_3$ was omitted from this reaction, indicating that the FC reaction between a suitably activated aromatic moiety and iminyl chloride is possible in HFIP even without additional promoters. Moreover, no arylation was observed when the analogous reaction of anisole—found *not* to work using our interrupted Schmidt/arylation protocol—was attempted. It is worth noting that this type of iminyl chloride is generally prepared and reacted in situ, underlining the attractiveness of making compounds such as **3a** through the presently reported process.[15]

The nitrilium ion was proposed as an intermediate in the Schmidt reaction by P. A. S. Smith 70 years ago. Since then, it

has been nearly exclusively used to react with water (to make amides or lactams) or with azide species (to form tetrazoles, either deliberately or as a nuisance byproduct). The present demonstration that this intermediate, either directly or through an iminyl halide species, can be leveraged for C−C bond formation extends the utility of Schmidt chemistry to afford synthetically useful iminium ions in addition to amides.

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Author Contributions

J.A. conceived the project and advised the experimentalists, M.C. and K.L. performed experiments, H.F.M. performed proof-of-concept experiments, J.A. and M.C. wrote the manuscript, and all of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Wrobleski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1−320.
(2) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320−323.
(3) Schmidt, K. F. *Ber. Dtsch. Chem. Ges. B* **1924**, *57*, 704−706.
(4) (a) Litkei, G.; Patonay, T. *Acta Chim. Hung.* **1983**, *114*, 47−56. (b) Zhang, F.-L.; Wang, Y.-F.; Lonca, G. H.; Zhu, X.; Chiba, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4390−4394. (c) Motiwala, H. F.; Charaschanya, M.; Day, V. W.; Aubé, J. *J. Org. Chem.* **2016**, *81*, 1593−1609.

(5) (a) Schinzer, D.; Bo, Y. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 687−688. (b) Schinzer, D.; Langkopf, E. *Synlett* **1994**, *1994*, 375−377. (c) Schinzer, D.; Abel, U.; Jones, P. G. *Synlett* **1997**, *1997*, 632−634. (d) Kang, K.-T.; Sung, T.-M.; Jung, H.-C.; Lee, J.-G. *Bull. Korean Chem. Soc.* **2008**, *29*, 1669−1670.

(6) (a) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831−2843. (b) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 943−946. (c) Sakane, S.; Matsumura, Y.; Yamamura, Y.; Ishida, Y.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 672−674.

(7) Takuwa, T.; Minowa, T.; Onishi, J. Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1717−1725.

(8) (a) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676−5688. (b) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 732−751.

(9) (a) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35−76. (b) Yorimitsu, H. *Chem. Rec.* **2017**, *17*, 1156−1167. (c) Meng, L.; Zeng, J.; Wan, Q. *Synlett* **2018**, *29*, 148−156.

(10) (a) Mo, Y.; Zhao, J.; Chen, W.; Wang, Q. *Res. Chem. Intermed.* **2015**, *41*, 5869−5877. (b) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Chem. - Eur. J.* **2016**, *22*, 2856−2881. (c) Susick, R. B.; Morrill, L. A.; Picazo, E.; Garg, N. K. *Synlett* **2017**, *28*, 1−11.

(11) (a) Medley, J. W.; Movassaghi, M. *Org. Lett.* **2013**, *15*, 3614−3617. (b) White, K. L.; Mewald, M.; Movassaghi, M. *J. Org. Chem.* **2015**, *80*, 7403−7411.

(12) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226−7232.

(13) (a) Courant, T.; Dagousset, G.; Masson, G. *Synthesis* **2015**, *47*, 1799−1856. (b) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599−4657. (c) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455−3460.

(14) Jurczak, J.; Kozluk, T.; Kulicki, W.; Pietraszkiewicz, M.; Szymanski, J. *Synthesis* **1983**, *1983*, 382.

(15) For recent alternative approaches to similarly reactive nitrilium ions, see: (a) Ramanathan, M.; Wang, Y.-H.; Liu, Y.-H.; Peng, S.-M.; Cheng, Y.-C.; Liu, S.-T. *J. Org. Chem.* **2018**, *83*, 6133−6141. (b) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J. *J. Org. Chem.* **2016**, *81*, 9020−9027.