

HETEROCYCLES, Vol. 99, No. 2, 2019, pp. 865 - 874. © 2019 The Japan Institute of Heterocyclic Chemistry  
Received, 12th October, 2018, Accepted, 31st October, 2018, Published online, 29th January, 2019  
DOI: 10.3987/COM-18-S(F)93

## VICINAL FUNCTIONALIZATION OF URACIL HETEROCYCLES WITH BASE ACTIVATION OF IODONIUM(III) SALTS

Naoko Takenaga,<sup>\*,†</sup> Shohei Ueda,<sup>‡</sup> Takumi Hayashi,<sup>‡</sup> Toshifumi Dohi,<sup>‡</sup> and  
Shinji Kitagaki<sup>†</sup>

<sup>†</sup>Faculty of Pharmacy, Meijo University, 150 Yagotoyama, Tempaku-ku, Nagoya, 468-8503, Japan. <sup>‡</sup>College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihigashi, Kusatsu, Shiga 525-8577, Japan. Corresponding author. Tel: +81-52-839-2706. E-mail: ntakenag@meijo-u.ac.jp (N. Takenaga)

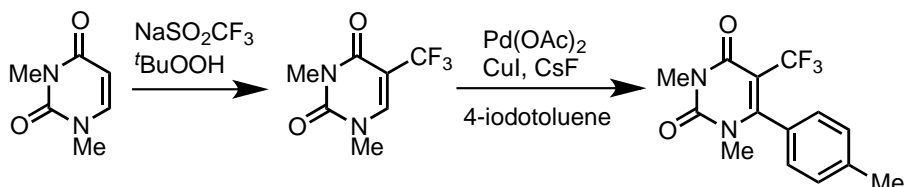
**Abstract** – We describe a new approach for the construction of bicyclic uracil systems and vicinal functionalization by utilizing uracil-iodonium(III) salts. Our method efficiently furnishes various multi-functionalized uracil derivatives in a single step.

This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday.

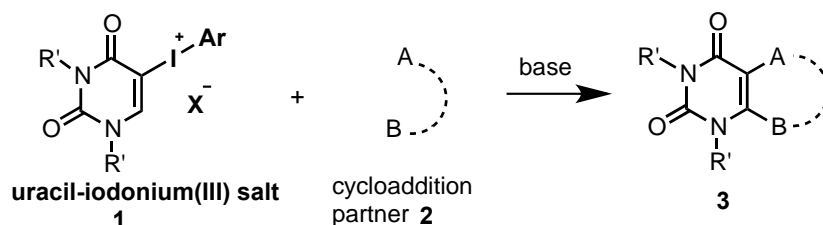
Uracil is an important structural unit that is incorporated into pharmaceutical intermediates and useful building blocks for bioactive compounds.<sup>1</sup> Functionalized uracils are typically prepared by heterocyclization involving multiple steps<sup>2</sup> or transition metal-catalyzed cross-coupling of halogenated or metallated uracils.<sup>3</sup> In recent years, direct C-H functionalization of uracils by arylation,<sup>4a-c</sup> alkenylation,<sup>4d</sup> acetoxylation,<sup>4e</sup> and trifluoromethylation,<sup>4f-h</sup> have been attempted with the aim of increasing the demand for step economy and byproduct reduce. Consecutive direct C-H functionalization at the C-5 and C-6 positions of the uracil ring is considered a suitable approach to obtain highly functionalized 5,6-disubstituted uracils. However, the only example of this strategy is the synthesis of 6-aryl-5-trifluoromethyluracil derivatives by two successive C-H functionalizations in a stepwise fashion, reported by Hocek and co-workers (Scheme 1A).<sup>4i</sup> While the aforementioned method represents a reliable route to vicinal difunctionalized uracils, a more efficient and complementary methodology is required for further advance of uracil functionalization and synthesis of new uracil derivatives. In this communication,

we report a new and direct method for accessing vicinal-functionalized uracils via single-step operation with base activation of uracil-iodonium(III) salts **1** (Scheme 1B).

**(A) Consecutive direct C-H functionalization (ref. 4i)**

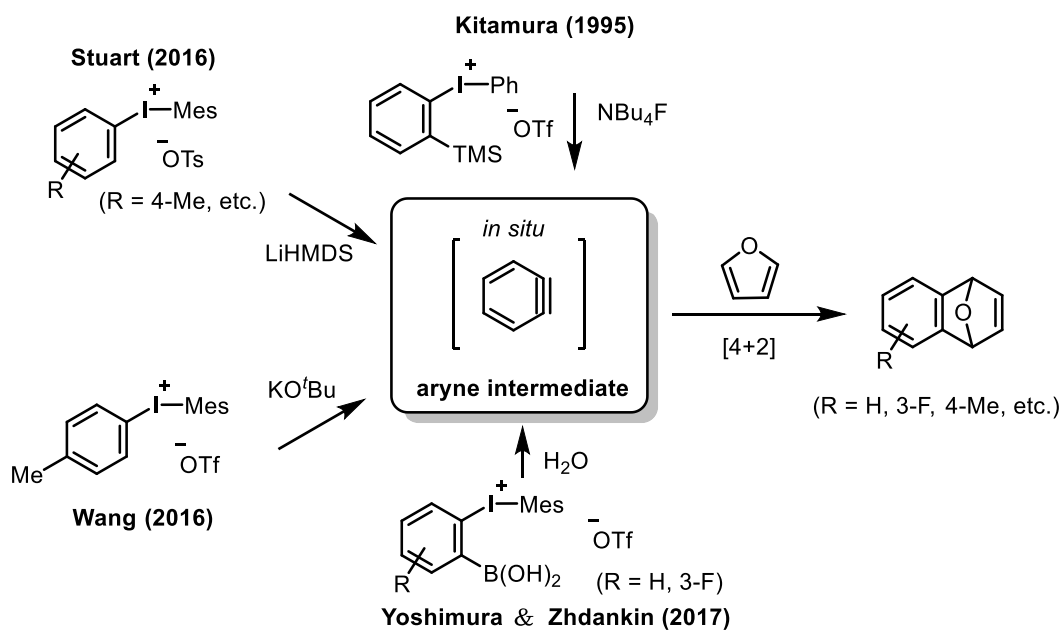


**(B) This work (our suggested strategy)**



**Scheme 1.** Reported vicinal functionalization of uracils (A) and our suggested strategy (B)

In 1995, Kitamura reported the preparation of phenyl[*o*-(trimethylsilyl)phenyl]iodonium(III) triflate, an efficient aryne precursor for trapping a series of furans (Figure 1),<sup>5e</sup> by the vicinal functionalization of benzene rings using hypervalent iodine compounds.<sup>5</sup>

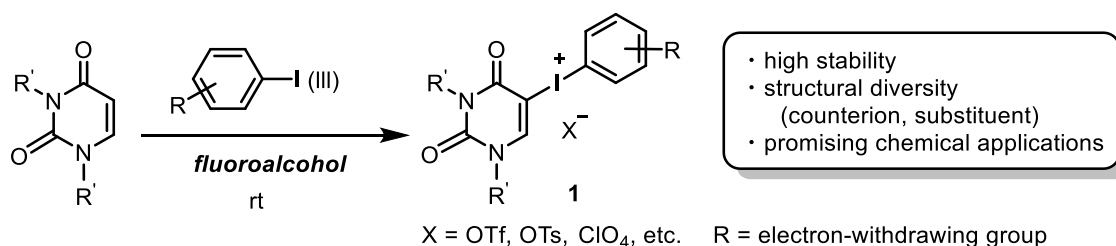


**Figure 1.** Reported iodonium(III) salts as aryne precursors and aryne trapping with furan (Mes = mesityl)

In 2016, Stuart<sup>5j</sup> and Wang<sup>5k</sup> independently discovered that arynes generated from diaryliodonium(III) salts by *ortho*-deprotonation and elimination of the hypervalent iodine group under basic conditions underwent cycloaddition with furans or *N*-arylation with secondary amides and amines. More recently, Yoshimura and Zhdankin demonstrated that pseudocyclic arylbenziodoxaborole triflates can serve as specific aryne precursors, and obtained various aryne adducts by utilizing this new synthetic module.<sup>5l</sup> In these transformations, hypervalent iodonium(III) salts<sup>6</sup> were utilized as promising aryne precursors<sup>5</sup> among various compounds for aryne chemistry.<sup>7,8</sup> The iodonium(III) strategy has also been extended to the generation of a highly strained cyclic alkyne,<sup>9</sup> bicyclo[2.2.1]hept-2-en-5-yne, from norbornadienyl iodonium(III) triflate.<sup>9a</sup>

Iodonium(III) salts incorporating a nucleobase or nucleoside moiety have recently appeared in the literature.<sup>10</sup> However, the hygroscopic nature of uracil-iodonium(III) salts renders their isolation and application difficult, leading to their gradual decomposition.<sup>10b</sup> Thus, the relationship between the stability and structure of these uracil-iodonium(III) salts has not been explored thus far. Consequently, the application of uracil-iodonium(III) salts is restricted to a few reactions such as palladium-catalyzed alkenylation<sup>10a</sup> and organocatalytic arylation of aldehydes.<sup>10b</sup>

We recently reported a facile synthesis of uracil-iodonium(III) salts **1** with various counterions (Scheme 2).<sup>11</sup> In this study, we found that the introduction of an electron-withdrawing group into the aryl moiety has beneficial for the isolation and prolonged storage of these salts. As a new application of this unique nucleobase synthetic module, the efficient vicinal functionalization of the uracil ring mediated by **1** is now examined. To the best of our knowledge, there has been no report on the one-step vicinal functionalization of the uracil ring and the successful generation of uracil cyclic alkyne species.



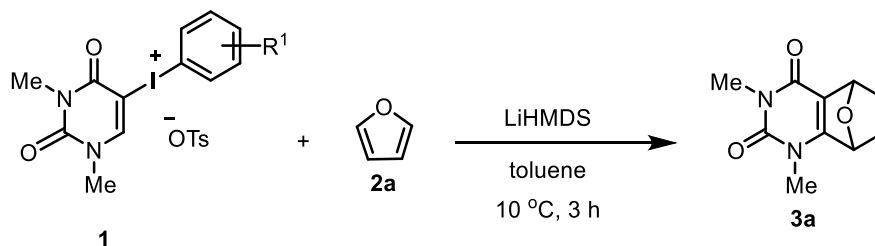
**Scheme 2.** Synthesis of uracil-iodonium(III) salts (our previous work)

We initially investigated the cycloaddition with furan **2a** employing stable uracil-iodonium(III) tosylate **1a**<sup>11</sup> bearing a 4-chlorophenyl group (Table 1). To our delight, when using lithium hexamethyldisilazide (LiHMDS) as the base in toluene, the corresponding bicyclic Diels-Alder adduct **3a** was obtained in 31% yield (Entry 1). Compound **3a** could be further converted into bioactive quinazoline-2,4-diones that are difficult to access by the conventional method from isatoic anhydride precursors.<sup>12</sup> Among the various

solvents tested, toluene was found to be the best for this reaction system. Further examination of the base (NaHMDS, LDA, NaO<sup>t</sup>Bu, <sup>s</sup>BuLi) did not lead to superior results.

In general, the chemical and physical properties of iodonium(III) salts strongly depend on the nature of the aryl moiety and the anionic counterpart. Hence, we next examined iodonium(III) tosylates bearing a variety of aryl moieties (Entries 2-7). While the use of 4-trifluoromethylphenyliodonium(III) tosylate **1b** was ineffective (Entry 2), tosylate **1c** bearing a 2-chlorophenyl group improved the yield of the cycloadduct **3a** (Entry 3). We then tested various 2-substituted phenyliodonium(III) tosylates, including 2,6-dichlorophenyl **1d** (Entry 4), 2-fluorophenyl **1e** (Entry 5), 2-trifluoromethoxyphenyl **1f** (Entry 6), and 2-trifluoromethylphenyl **1g** (Entry 7). The product yield was most promising when using **1g** with an *ortho* electron-withdrawing group (Entry 7). Regarding the anionic counterpart, replacing the tosylate with triflate, trifluoroacetate, and perchlorate significantly decreased the product yield. A higher concentration of substrate **1g** was used with the aim of accelerating the reaction, but the product yield was not improved (Entry 8).

**Table 1.** Optimization of furan addition to uracil ring with base activation of iodonium(III) salt **1**<sup>a</sup>

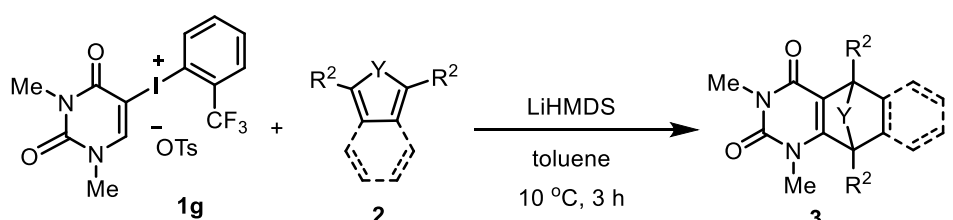


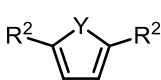
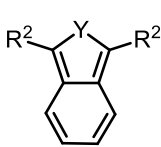
Entry	I(III)	R <sup>1</sup>	Yield (%) <sup>b</sup>
1	<b>1a</b>	4-Cl	31
2	<b>1b</b>	4-CF <sub>3</sub>	20
3	<b>1c</b>	2-Cl	37
4	<b>1d</b>	2, 6-Cl <sub>2</sub>	24
5	<b>1e</b>	2-F	22
6	<b>1f</b>	2-OCF <sub>3</sub>	28
7	<b>1g</b>	2-CF <sub>3</sub>	40 <sup>c</sup>
8 <sup>d</sup>	<b>1g</b>	2-CF <sub>3</sub>	19

<sup>a</sup> Reactions were performed using 2 equiv of LiHMDS and 5.5 equiv of furan **2a** at 10 °C in toluene (0.1 M). <sup>b</sup> Determined by <sup>1</sup>H-NMR. <sup>c</sup> Isolated yield. <sup>d</sup> Reaction was performed using 0.2 M concentration of substrate **1**.

With the optimal reaction conditions in hand (Table 1, Entry 7), we then explored the scope of this [4+2] cyclization (Table 2). The reaction of uracil-iodonium(III) salt **1g** and 2,5-dimethylfuran **2b** proceeded to afford the product in an acceptable yield (Entry 2). When *N*-substituted pyrroles **2c-e** were subjected to the reaction conditions, the desired [4+2] cycloaddition products **3c-e** also obtained (Entries 3-5). The reaction of diphenylisobenzofuran **2f** did not proceed smoothly at 10 °C, but when the temperature was increased to 40 °C, the corresponding annulated product **3f** was obtained in good yield (Entry 6). Note that these reactions did not proceed when 4-chlorophenyl-iodonium(III) tosylate **1a** was used instead of **1g**.

**Table 2.** [4+2] Cycloaddition using uracil-iodonium(III) salt **1g**<sup>a</sup>

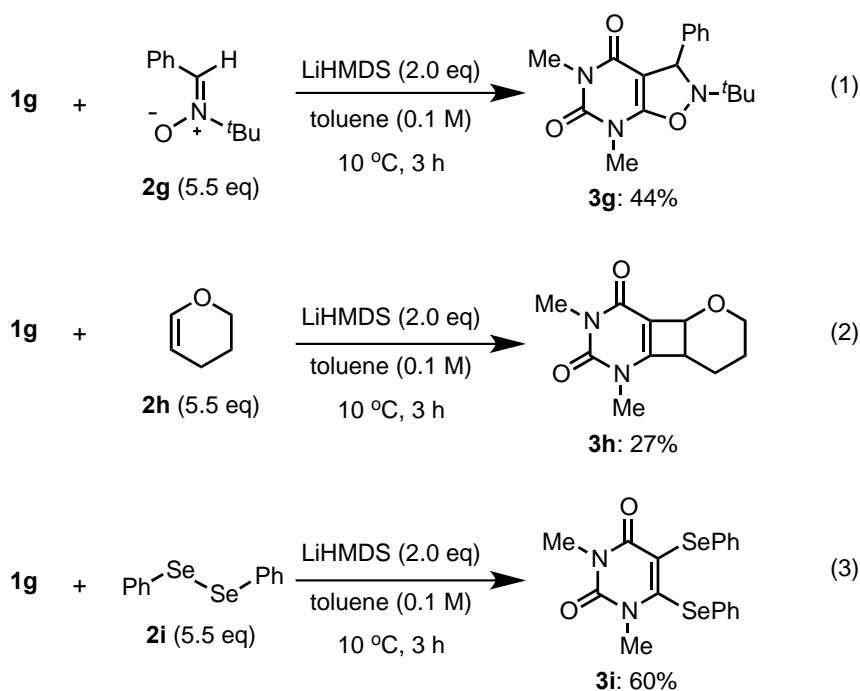


Entry	<b>2</b>	R <sup>2</sup>	Y	<b>3</b>	Yield (%) <sup>b</sup>
					
1	<b>2a</b>	H	O	<b>3a</b>	40
2	<b>2b</b>	Me	O	<b>3b</b>	42
3	<b>2c</b>	H	NPh	<b>3c</b>	38
4	<b>2d</b>	H	NBoc	<b>3d</b>	45
5	<b>2e</b>	H	N-4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3e</b>	42
6 <sup>c</sup>		Ph	O	<b>3f</b>	55

<sup>a</sup> Reactions were performed using 2 equiv of LiHMDS and 5.5 equiv of arynophile **3** at 10 °C in toluene (0.1 M). <sup>b</sup> Isolated yield. <sup>c</sup> Reaction was performed at 40 °C.

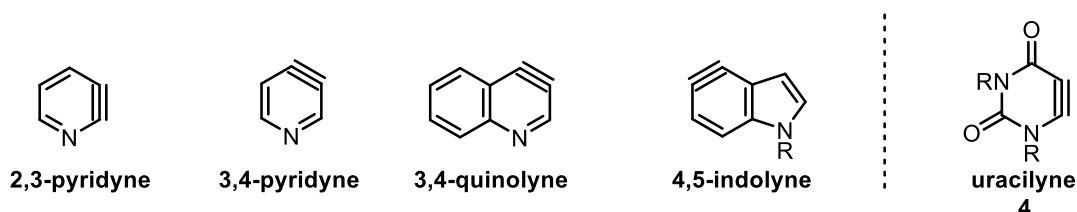
Although further investigation is required,<sup>13</sup> uracil-iodonium(III) salt **1g** could be used for other types of cycloadditions as well (see Scheme 3 for selected examples). *N*-*tert*-Butyl- $\alpha$ -phenyl nitrone **2g**<sup>8k</sup> furnished a [3+2] annulated product **3g** (Eq. 1), which is a medically privileged scaffold. The

application of 3,4-dihydro-2*H*-pyran **2h**<sup>8l</sup> as an alkynophile afforded the [2+2] annulated product **3h** (Eq. 2). When diphenyldiselenide **2i**<sup>8m</sup> was utilized,  $\sigma$ -bond insertion, which is characteristic of the aryne reactivity, occurred to give the 5,6-difunctionalized product **3i** (Eq. 3).



**Scheme 3.** Selected examples of other vicinal functionalizations of uracil ring utilizing uracil-iodonium(III) salt **1g** ([3+2] and [2+2] cycloadditions, and  $\sigma$ -bond insertion)

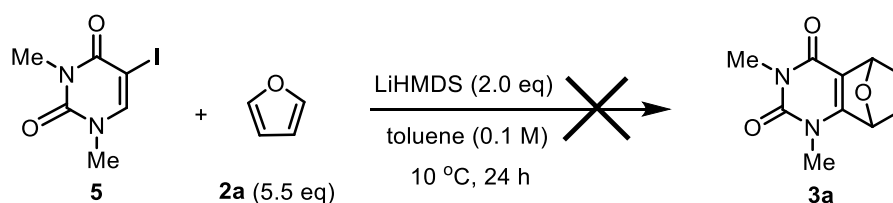
Based on the experimental results, we propose that the reaction mechanism involves the formation of uracilyne **4** (Figure 2). First, LiHMDS abstracts the  $C_{sp^2}$  uracil hydrogen of iodonium(III) salt **1**. Because of the exceptionally high leaving group ability of hypervalent iodine(III),<sup>6i</sup> facile elimination of 2-iodobenzotrifluoride occurs to generate a uracil-heteroaryne analog, the so-called “uracilyne” **4**. This reactive alkyne species **4**, having a highly strained and distorted  $C\equiv C$  bond,<sup>14</sup> reacts with the trapping agent **2** regioselectively to afford the corresponding cycloadduct **3**.



**Figure 2.** Reported heteroarynes and uracil-heteroaryne analog **4**

To the best of our knowledge, there is no report on the successful generation of cyclic uracil alkyne **4** (uracilyne, Figure 2) or its vicinal functionalization. Aryne chemistry offers a strategic advantage for the multi-functionalization of aromatic rings in a single synthetic operation. Heteroaromatic versions of arynes,<sup>15</sup> such as pyridyne and indolyne (Figure 2), are attractive tools for the synthesis of multi-functionalized heteroarene derivatives.<sup>16</sup> However, in contrast to benzyne chemistry, the synthetic utilization of heteroarynes is not fully explored. As per the literature, the treatment of halouracils with a variety of strong bases failed to generate **4**.<sup>15a</sup> In a more recent effort, Garg and co-workers attempted to generate pyrimidyne from silyltriflate precursors but were unsuccessful.<sup>16g</sup>

To shed further light on the specific application of uracil iodonium(III) salts, we compared the reactivity of a halogenated uracil, as shown in Scheme 4. The reaction of 5-iodouracil **5**, instead of iodonium(III) salt **1**, with furan **2a** under our optimized conditions did not proceed, and cycloadduct **3a** was not obtained at all.



**Scheme 4.** Unsuccessful cycloaddition using 5-iodouracil **5**

In summary, we have succeeded in the vicinal functionalization of the uracil ring in a single synthetic operation by utilizing uracil-iodonium(III) salts with basic activation.<sup>17</sup> The reactive intermediates of this reaction are believed to include a highly strained heterocyclic alkyne species, uracilyne **4**. This new finding would trigger the utilization of uracilyne as a useful building block in organic synthesis. Further investigation on the rationalization and utilization of uracilyne generation is in progress in our laboratory.

## ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Number 16K18854. T.D. acknowledges the support from Ritsumeikan Global Innovation Research Organization (R-GIRO) project.

## REFERENCES AND NOTES

- (a) A. Pałasz and D. Cież, *Eur. J. Med. Chem.*, 2015, **97**, 582; (b) H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. N. Lehrman, Ft. C. Gallo, D. Bolognesi, D. W. Barry, and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1985, **82**, 7096; (c) E. De Clercq, J. Descamps, P. De Somer, P. J. Barr, A. S. Jones, and R. T. Walker, *Proc. Natl. Acad. Sci. U.S.A.*, 1979, **76**, 2947; (d) N. J. Greco and Y.

- Tor, *J. Am. Chem. Soc.*, 2005, **127**, 10784.
2. (a) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, 1958, **80**, 5744; (b) C. Kaiser and A. Burger, *J. Org. Chem.*, 1959, **24**, 113.
  3. (a) L. A. Agrofoglio, I. Gillaizeau, and Y. Saito, *Chem. Rev.*, 2003, **103**, 1875; (b) G. T. Crisp and B. L. Flynn, *Tetrahedron Lett.*, 1990, **31**, 1347; (c) Y. Ding, J.-L. Girardet, Z. Hong, S. Z. Shaw, and N. Yao, *Heterocycles*, 2006, **68**, 521; (d) M. J. G. Moa, P. Besada, and C. Teran, *Synthesis*, 2006, 3973.
  4. (a) K. H. Kim, H. S. Lee, and J. N. Kim, *Tetrahedron Lett.*, 2011, **52**, 6228; (b) M. Cernova, I. Cerna, R. Pohl, and M. Hocek, *J. Org. Chem.*, 2011, **76**, 5309; (c) M. Cernova, R. Pohl, and M. Hocek, *Eur. J. Org. Chem.*, 2009, 3698; (d) Y.-Y. Yu and G. I. Georg, *Chem. Commun.*, 2013, **49**, 3694; (e) H. S. Lee, S. H. Kim, and J. N. Kim, *Bull. Korean Chem. Soc.*, 2010, **31**, 238; (f) Y. N. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, and P. S. Baran, *Proc. Natl. Acad. Sci. U.S.A.*, 2011, **108**, 14411; (g) D. Uraguchi, K. Yamamoto, Y. Ohtsuka, K. Tokuhisa, and T. Yamakawa, *Appl. Catal., A*, 2008, **342**, 137; (h) D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224; consecutive functionalization; (i) M. Čerňová, R. Pohl, B. Klepetářová, and M. Hocek, *Heterocycles*, 2014, **89**, 1159.
  5. (a) D. Del Mazza and M. G. Reinecke, *J. Org. Chem.*, 1988, **53**, 5799; (b) M. G. Reinecke, D. Del Mazza, and M. Obeng, *J. Org. Chem.*, 2003, **68**, 70; (c) M. G. Reinecke and D. Del Mazza, *J. Org. Chem.*, 1989, **54**, 2142; (d) T. Kitamura, M. Yamane, K. Inoue, M. Todaka, N. Fukatsu, Z. Meng, and Y. Fujiwara, *J. Am. Chem. Soc.*, 1999, **121**, 11674; (e) T. Kitamura and M. Yamane, *J. Chem. Soc., Chem. Commun.*, 1995, 983; (f) T. Kitamura, K. Gondo, and J. Oyamada, *J. Am. Chem. Soc.*, 2017, **139**, 8416; (g) T. Akiyama, Y. Imasaki, and M. Kawanisi, *Chem. Lett.*, 1974, **3**, 229; (h) J. I. G. Cadogan, A. G. Rowley, J. T. Sharp, B. Sledzinski, and N. H. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1072; (i) S. K. Sundalam, A. Nilova, T. L. Seidl, and D. R. Stuart, *Angew. Chem. Int. Ed.*, 2016, **55**, 8431; (j) D. R. Stuart, *Synlett*, 2017, **28**, 275; (k) M. Wang and Z. Huang, *Org. Biomol. Chem.*, 2016, **14**, 10185; (l) A. Yoshimura, J. M. Fuchs, K. R. Middleton, A. V. Maskaev, G. T. Rohde, A. Saito, P. S. Postnikov, M. S. Yusubov, V. N. Nemykin, and V. V. Zhdankin, *Chem. Eur. J.*, 2017, **23**, 16738.
  6. (a) A. Yoshimura and V. V. Zhdankin, *Chem. Rev.*, 2016, **116**, 3328; (b) T. Dohi and Y. Kita, *Curr. Org. Chem.*, 2016, **20**, 580; (c) Y. Li, D. P. Hari, M. V. Vita, and J. Waser, *Angew. Chem. Int. Ed.*, 2016, **55**, 4436; (d) S. V. Kohlhepp and T. Gulder, *Chem. Soc. Rev.*, 2016, **45**, 6270; (e) R. M. Romero, T. H. Woeste, and K. Muniz, *Chem. Asian J.*, 2014, **9**, 972; (f) M. Ochiai, *J. Organomet. Chem.*, 2000, **611**, 494; (g) J. Charpentier, N. Fruh, and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (h) R. Narayan, S. Manna, and A. P. Antonchick, *Synlett*, 2015, **26**, 1785; (i) T. Okuyama, T. Takino, T. Sueda, and M. Ochiai, *J. Am. Chem. Soc.*, 1995, **117**, 3360.



7. (a) H. Heaney, *Chem. Rev.*, 1962, **62**, 81; (b) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550; (c) R. Karmakar and D. Lee, *Chem. Soc. Rev.*, 2016, **45**, 4459; (d) J.-A. García-López and M. F. Greaney, *Chem. Soc. Rev.*, 2016, **45**, 6766; (e) H. Pellissier and M. Santelli, *Tetrahedron*, 2003, **59**, 701.
8. (a) K. C. Caster, C. G. Keck, and R. D. Walls, *J. Org. Chem.*, 2001, **66**, 2932; (b) M. Uchiyama, T. Miyoshi, Y. Kajihara, T. Sakamoto, Y. Otani, T. Ohwada, and Y. Kondo, *J. Am. Chem. Soc.*, 2002, **124**, 8514; (c) V. Diemer, M. Begaud, F. R. Leroux, and F. Colobert, *Eur. J. Org. Chem.*, 2011, 341; (d) M. Stiles, U. Burckhardt, and G. Freund, *J. Org. Chem.*, 1967, **32**, 3718; (e) R. S. Berry, J. Clardy, and M. E. Schafer, *J. Am. Chem. Soc.*, 1964, **86**, 2738; (f) L. Friedman and F. M. Logullo, *J. Org. Chem.*, 1969, **34**, 3089; (g) G. Wittig and R. W. Hoffmann, *Org. Synth.*, 1967, **47**, 4; (h) S. E. Whitney, M. Winters, and B. Rickborn, *J. Org. Chem.*, 1990, **55**, 929; (i) S. Nakazawa, T. Kiyosawa, K. Hirakawa, and H. Kato, *J. Chem. Soc., Chem. Commun.*, 1974, 621; (j) Y. Himeshima, T. Sonoda, and H. Kobayashi, *Chem. Lett.*, 1983, **12**, 1211; (k) T. Matsumoto, T. Sohma, S. Hatazaki, and K. Suzuki, *Synlett*, 1993, 843; (l) V. R. Yedulla, P. Pradhan, L. Yang, and M. K. Lakshman, *Eur. J. Org. Chem.*, 2015, 750; (m) F. T. Toledo, H. Marques, J. V. Comasseto, and C. Raminelli, *Tetrahedron Lett.*, 2007, **48**, 8125.
9. (a) T. Kitamura, M. Kotani, T. Yokoyama, and Y. Fujiwara, *J. Org. Chem.*, 1999, **64**, 680; (b) M. Fujita, Y. Sakanishi, W. H. Kim, and T. Okuyama, *Chem. Lett.*, 2002, 908; (c) T. Lee, J. Jeon, K. H. Song, I. Jung, C. Baik, K.-M. Park, S. S. Lee, S. O. Kang, and J. Ko, *J. Chem. Soc., Dalton Trans.*, 2004, 933; (d) Y. Fujita, W. H. Kim, Y. Sakanishi, K. Fujiwara, S. Hirayama, T. Okuyama, Y. Ohki, K. Tatsumi, and Y. Yoshioka, *J. Am. Chem. Soc.*, 2004, **126**, 7548.
10. (a) K. R. Roh, J. Y. Kim, and Y. H. Kim, *Tetrahedron Lett.*, 1999, **40**, 1903; (b) Q. Y. Toh, A. McNally, S. Vera, N. Erdmann, and M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 3772; (c) M. Bielawski, J. Malmgren, L. M. Pardo, Y. Wikmark, and B. Olofsson, *ChemistryOpen*, 2014, **3**, 19; (d) S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.*, 2015, **137**, 1416; (e) S. Altomonte, S. Telu, S. Lu, and V. W. Pike, *J. Org. Chem.*, 2017, **82**, 11925.
11. N. Takenaga, S. Ueda, T. Hayashi, T. Dohi, and S. Kitagaki, *Heterocycles*, 2018, **97**, 1248.
12. J. J. McNally and J. B. Press, *J. Org. Chem.*, 1991, **56**, 245.
13. Only one regioisomer of annulated product **3g** was formed, and the structure of which is confirmed by NOE measurement. This regioselectivity trend of the [3+2] substrate **2g** is consistent with prior observations (ref. 8k). Similarly, dihydropyran **2h** reacted regioselectively (ref. 8l).
14. A distortion/interaction model was recently proposed for predicting the regioselectivity of arynes in the reaction with a nucleophile. See: (a) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G.-Y. J. Im, N. K. Garg, and K. N. Houk, *J. Am. Chem. Soc.*, 2010, **132**, 1267; (b) S. M. Bronner, J. L. Mackey, K.

- N. Houk, and N. K. Garg, *J. Am. Chem. Soc.*, 2012, **134**, 13966; (c) J. M. Medina, J. L. Mackey, N. K. Garg, and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 15798; (d) E. Picazo, K. N. Houk, and K. N. Garg, *Tetrahedron Lett.*, 2015, **56**, 3511.
15. For reviews regarding heteroaromatic arynes, see: (a) M. G. Reinecke, *Tetrahedron*, 1982, **38**, 427; (b) T. Kauffmann and R. Wirthwein, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 20.
16. Generation of pyridyne and indolyne: (a) S. M. Bronner, K. B. Bahnck, and N. K. Garg, *Org. Lett.*, 2009, **11**, 1007; (b) G-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, and N. K. Garg, *J. Am. Chem. Soc.*, 2010, **132**, 17933; (c) A. E. Goetz and N. K. Garg, *Nat. Chem.*, 2013, **5**, 54; (d) N. Saito, K. Nakamura, S. Shibano, S. Ide, M. Minami, and Y. Sato, *Org. Lett.*, 2013, **15**, 386; (e) M. A. Walters and J. J. Shay, *Synth. Commun.*, 1997, **27**, 3573; (f) Y. Fang and R. C. Larock, *Tetrahedron*, 2012, **68**, 2819; (g) J. M. Medina, M. K. Jackl, R. B. Susick, and N. K. Garg, *Tetrahedron*, 2016, **72**, 3629.
17. **Representative experimental procedure** (Table 2, entry 1): In a flame-dried flask, under nitrogen, to a mixture of iodonium salt **1g** (0.50 mmol) and furan **2a** (2.75 mmol, 5.5 equiv) in toluene (5 mL, 0.1 M) in ice-cooled bath maintained at 10 °C, LiHMDS (0.77 mL (1.3 M in toluene), 1.0 mmol, 2.0 equiv) was dropwise added by syringe, and the mixture was stirred for 3 h. After completion of the reaction checked by TLC, the reaction mixture was quenched with an aqueous solution of ammonium chloride. The resultant biphasic solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried with solid sodium sulfate, and then concentrated. The residue was purified by column chromatography on silica gel using hexane-EtOAc as eluent to give 1,3-dimethyl-5,8-dihydro-5,8-epoxyquinazoline-2,4(1*H*,3*H*)-dione **3a** as white solid (40%). mp 140-141 °C. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 7.34 (1H, dd, *J* = 5.6, 1.6 Hz), 7.01 (1H, dd, *J* = 5.2, 2.0 Hz), 5.83-5.92 (1H, m), 5.58-5.66 (1H, m), 3.46 (3H, s), 3.27 (3H, s) ppm; <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): 170.5, 158.2, 151.5, 148.0, 138.8, 118.6, 81.4, 81.0, 33.4, 28.2 ppm; IR: 2967, 2928, 1662, 1466, 1389, 1361, 1151 cm<sup>-1</sup>; HRMS (FAB): calcd for C<sub>10</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 207.0770, found: 207.0771. The reactions of other substrates **2b-i** shown in Table 2 and Scheme 3 were performed by same experimental procedures.