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Dual Roles of Methyl Ketones in Radziszewski-Type Reaction: Formal [2 + 1 + 1 + 1] Synthesis of 1,2,5-Trisubstituted Imidazoles

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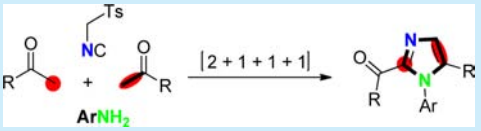
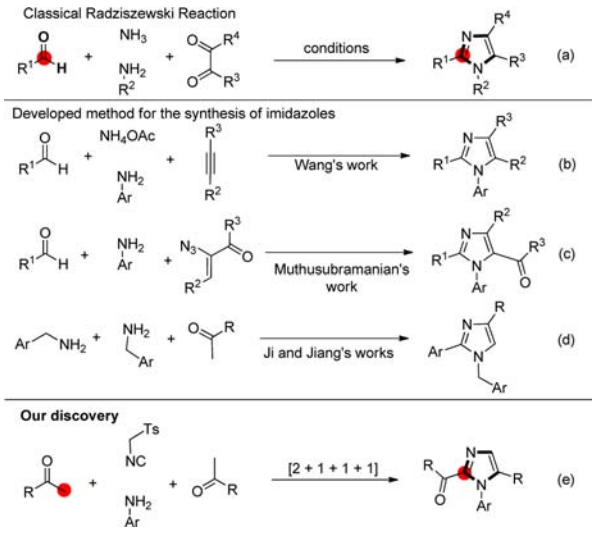
Supporting Information

ABSTRACT: A highly efficient molecular iodine mediated Radziszewski-type reaction of methyl ketones, anilines, and tosylmethyl isocyanide has been developed. This protocol represents an elegant molecular fragment assembly of imidazoles via a formal [2 + 1 + 1 + 1] annulation. It is the first example where methyl ketones serve as the α-dicarbonyl compounds and aldehydes in Radziszewski-type reactions.



Imidazoles are privileged five-membered nitrogen heterocycles. They are found in a wide range of biologically active molecules[1] and can act as organocatalysts,[2] ionic liquids,[3] and precursors of N-heterocyclic carbenes.[4] The Radziszewski reaction,[5] which involves the condensation of an α-dicarbonyl compound, an aldehyde, and 2 equiv of dry ammonia (Scheme 1a), is the only reaction of industrial importance for the production of imidazole derivatives.[6] Over the past few years, significant progress has been made in development of the Radziszewski reaction, but most of the reported Radziszewski reactions have been limited to 1,2-diketones and aldehydes.[7] Increasing attention has focused on the use of the Radziszewski reaction to develop new methods for the construction of substituted imidazole compounds.[8] Recently, Wang's group disclosed an expedient route to 2,4,5-trisubstituted imidazoles via pivalic acid promoted 1,2-diketone generated in situ from internal alkynes (Scheme 1b).[9] Muthusubramanian et al. reported the use of α-azido chalcones instead of 1,2-diketones to construct polysubstituted imidazoles (Scheme 1c).[10] Jiang[11a] and Ji[11b] independently demonstrated that aryl methyl ketones and benzylamines can replace 1,2-diketones and aldehydes in the preparation of highly substituted imidazoles (Scheme 1d). However, to the best of our knowledge, there have been no reports of Radziszewski reactions with methyl ketones replacing both the α-dicarbonyl compound and the aldehyde. Here, we report a facile and efficient approach to the formation of substituted imidazoles via a formal [2 + 1 + 1 + 1] annulation from readily available methyl ketones, anilines, and tosylmethylisocyanide (TosMIC) (Scheme 1e).

Scheme 1. Radziszewski Reaction



Recently, we developed a Povarov-type formal [3 + 2 + 1] cycloaddition reaction for the direct synthesis of substituted quinolines from methyl ketones, arylamines, and styrenes, involving the key intermediate of *C*-acylimines generated in situ.[12] Inspired by these results, we attempted to use the Van Leusen reaction, which is a formal [3 + 2] cycloaddition reaction, between a *C*-acylimine and TosMIC for the preparation of imidazoles.[13] However, the Radziszewski product was obtained as the main product instead of the Van Leusen product. This indicated that we had discovered a new role for the Van Leusen reagent, in which it serves as an amino surrogate. First, we treated acetophenone (**1a**, 1.0 mmol), *p*-toluidine (**2a**, 1.0 mmol), and TosMIC (**3**, 1.5 mmol) with I_2 (1.6 mmol) in DMSO (2 mL) at 100 °C; the 1,2,5-trisubstituted imidazole (**4a**) was isolated in 43% yield (Table 1, entry 1). The structure of **4a** was unambiguously confirmed using X-ray crystallography (Supporting Information, Figure S2). This unexpected product prompted us to investigate the reaction parameters in greater detail to evaluate their impact on the reaction outcome. When the **1a**/**2a**/**3** molar ratios were 2:1:1, the reaction proceeded smoothly in DMSO using I_2 (1.6 mmol) in 3 h at 100 °C to afford the Radziszewski product **4a** in 72% yield (Table 1, entry 3). Brønsted acids can accelerate

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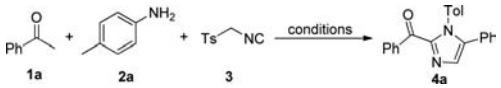
Table 1. Optimization of the Reaction Conditions[a]



entry	I_2 (mmol)	3 (mmol)	acid (0.5 mmol)	temp (°C)	yield[b] (%)
1	0.8	0.75		100	43[c]
2	1.6	0.75		100	67
3	1.6	0.5		100	72
4	1.6	1.0		100	61
5	1.6	0.5	CF_3SO_3H	100	67
6	1.6	0.5	PTSA·H_2O	100	69
7	1.6	0.5	HOAc	100	71
8	1.6	0.5	CH_3SO_3H	100	63
9	1.6	0.5	TFA	100	68
10	1.6	0.5	H_2SO_4	100	43
11	1.6	0.5	HCl	100	47
12	1.6	0.5	PhCOOH	100	62
13	1.6	0.5		80	48
14	1.6	0.5		90	56
15	1.6	0.5		110	76
16	1.6	0.5		120	51
17	0.3	0.5		110	51
18	0.5	0.5		110	72
19	**0.8**	**0.5**		**110**	**80**
20	1.0	0.5		110	78

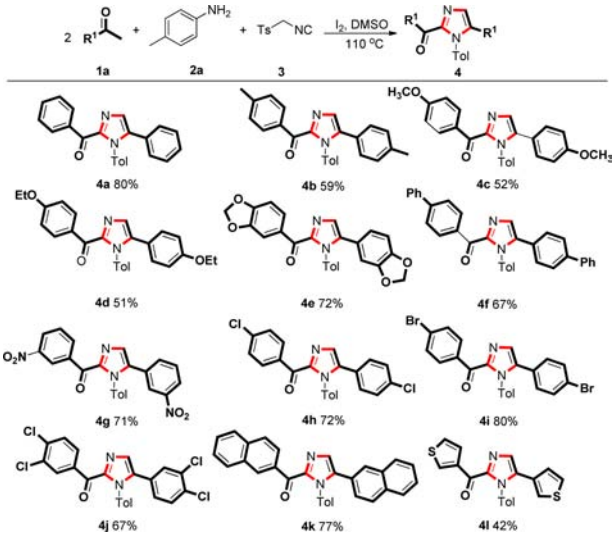
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), DMSO (2 mL). [b]Isolated yields. [c]**1a** (0.5 mmol).

the hydrolyses of TosMIC,[14] but a series of acids, namely CF_3SO_3H, PTSA·H_2O, HOAc, CH_3SO_3H, TFA, H_2SO_4, HCl, and PhCOOH, had no positive impact on the outcome of the reaction (Table 1, entries 5−12). These results suggest that additional acid could not enhance the catalytic efficiency of I_2. A range of different temperatures were tested to improve the yield (Table 1, entries 13−16), and 110 °C was identified as the optimum temperature for this four-component reaction. The yield of **4a** increased when the amount of I_2 was decreased to 0.8 mmol (Table 1, entry 19).

With the optimized conditions in hand, the generality and scope of the I_2-promoted four-component reaction were explored. The reaction had a wide substrate scope in terms of the aromatic ketone unit (Scheme 2). Aryl methyl ketones bearing electron-neutral (4-H), electron-rich (e.g., 4-Me, 4-OMe, 4-OEt, 3,4-OCH_2O), and electron-deficient (e.g., 4-Ph, 3-NO_2) phenyl rings were successfully converted to the corresponding products in moderate to good yields (51−80%; **4a−g**). The optimized conditions were mild enough to be compatible with a broad range of halogenated (e.g., 4-Cl, 4-Br, 3,4-Cl_2) substrates (67−80%; **4h−j**), which provided the possibility for further functionalization. The sterically hindered 2-naphthyl methyl ketone provided the expected product **4k** in 77% yield. The desired imidazole was obtained in moderate yield from a heteroaryl methyl ketone (42%; **4l**). However, no products was observed under the standard conditions when acetone was used as a substrate.

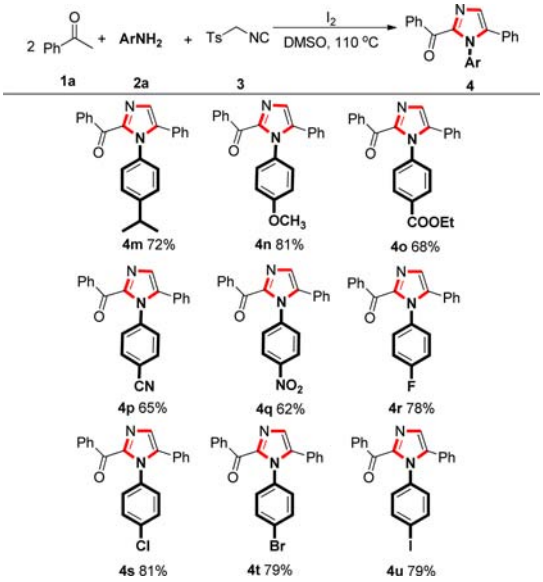
The scope of this reaction was then extended to a variety of substituted anilines; the desired products were obtained in satisfactory yields (Scheme 3). Both electron-rich and electron-deficient anilines were smoothly converted to the desired products (62−81%; **4m−q**). In general, aromatic amines containing electron-rich groups were more reactive than those bearing electron-deficient groups. Substrates bearing

Scheme 2. Scope of Methyl Ketones[a]



[a]Isolated yield.

Scheme 3. Scope of Arylamine[a]



[a]Isolated yield.

halogen substituents were well tolerated, and the corresponding halo-substituted products were isolated in good yields (78−81%; **4r−u**). However, no products was observed under the standard conditions when *n*-butylamine was used as a substrate.

With the scope of the method established, the reaction mechanism was investigated. When the acetophenone substrate was replaced with α-iodoacetophenone (**1aa**), the desired product **4a** was obtained in good yields, both with and without I_2 (Scheme 4a). The hydrated species **1ac** also reacted with **2a** and **3** in the presence of additional I_2, and **4a** was obtained in 48% yield (Scheme 4b). These results clearly confirm that **1aa** and phenylglyoxal (**1ab**) were the key intermediates in this transformation. The *C*-acylimine **5n** was subjected to the standard conditions and gave the desired product **4n** in 51% yield (Scheme 4c). This result shows that **5n** was the crucial intermediate in the process. However, the Radziszewski product **4n** was not detected when the reaction of **5n** with

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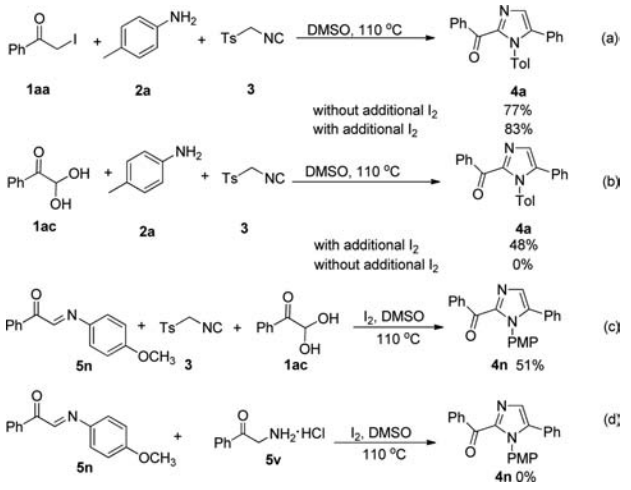
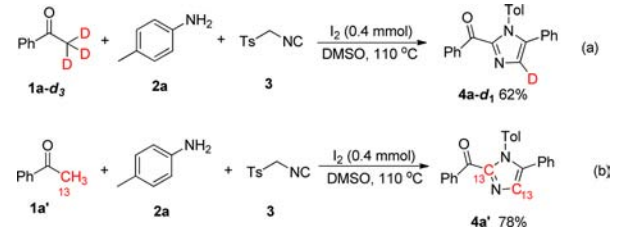
Scheme 4. Control Experiments



α-aminoacetophenone hydrochloride (**5v**) was performed under the standard conditions (Scheme 4d); this excludes the possibility of the formal [3 + 2] cycloaddition of two types of *C*-acylimine.

The reaction mechanism of this transformation was investigated in greater depth by performing D-labeling (Scheme 5a) and ^{13}C-labeling (Scheme 5b) experiments under the

Scheme 5. Control Experiments

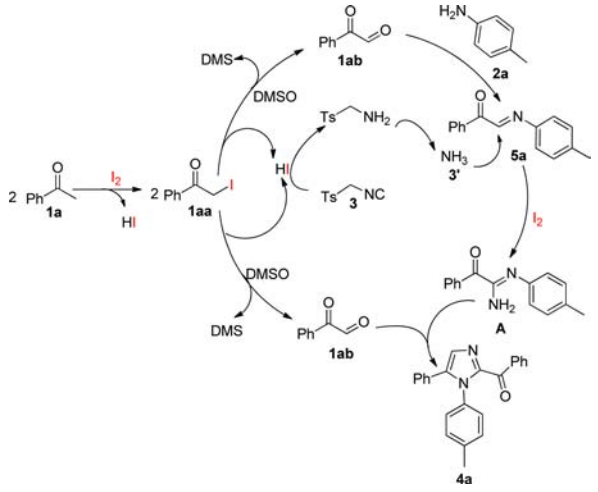


optimized conditions using acetophenone-β,β,β-d_3 and acetophenone-β-^{13}C, respectively, as the substrates. The corresponding desired products **4a**-d_1 and **4a**′ were obtained in good yields. Taken together, these experimental results show that methyl ketones provided all the carbons of the imidazole ring.

On the basis of the above results and previous work,[15] a possible mechanism is proposed that uses the reaction of acetophenone (**1a**), *p*-toluidine (**2a**), and TosMIC (**3**) as an example (Scheme 6). The initial reaction of I_2 with **1a** results in the formation of α-iodoacetophenone (**1aa**), which is then converted to phenylglyoxal (**1ab**) with release of HI via Kornblum oxidation in the presence of DMSO. The reaction of *p*-toluidine (**2a**) with the aldehyde group of **1ab** then gives the *C*-acylimine **5a**. Then **5a** reacts with the amine **3**′ formed in situ from **3** and HI[14] to afford intermediate **A** via an in situ cross-trapping process.[16] Finally, intermediate **A** participates in cyclocondensation[9] with another **1ab** molecule to provide the desired product **4a**.

We investigated the cross-coupling reaction using acetophenone (**1a**, 0.5 mmol), 1-(*p*-tolyl)ethanone (**1b**, 0.5 mmol), **2a**, and **3** under the standard conditions (Supporting Information, Scheme S2) to support our mechanism. According to our proposed reaction mechanism, the reaction of equimolar amounts of **1a** and **1b** would give three or four imidazole products. All of the products were successfully identified by

Scheme 6. Possible Mechanism



HRMS analysis of the crude reaction extract; this clearly confirms our proposed mechanism (Supporting Information, Figure S1).

In summary, we have developed a novel I_2-mediated formal [2 + 1 + 1 + 1] synthesis of 1,2,5-trisubstituted imidazoles from methyl ketones, anilines, and TosMIC in which the methyl ketones play dual roles as α-dicarbonyl compounds and aldehydes in the Radziszewski-type reaction. Initial studies of the mechanism suggest that the reaction proceeds via a key *C*-acylimine intermediate and I_2 plays an important role in the self-sorting tandem reaction. Further studies of applications of this *C*-acylimine cycloaddition are currently underway in our laboratory, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00607.

Experimental procedures, product characterization, crystallographic data, and ^{1}H and ^{13}C NMR spectra (PDF)
X-ray crystallographic data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sarshar, S.; Zhang, C. Z.; Moran, E. J.; Krane, S.; Rodarte, J. C.; Benbatoul, K. D.; Dixon, R.; Mjalli, A. M. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2599. (b) Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311. (c) Black, J. W.; Durant, G. I.; Emmett, J.

DOI: 10.1021/acs.orglett.6b00607
Org. Lett. 2016, 18, 1686−1689

C.; Ganellin, C. R. *Nature* **1974**, *248*, 65. (d) Koch, P.; Bäuerlein, C.; Jank, H.; Laufer, S. *J. Med. Chem.* **2008**, *51*, 5630.
(2) (a) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740. (b) Zhang, Z. F.; Xie, F.; Jia, J.; Zhang, W. B. *J. Am. Chem. Soc.* **2010**, *132*, 15939. (c) Li, Y. M.; Giulionatti, M.; Houghten, R. A. *Org. Lett.* **2010**, *12*, 2250.
(3) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667.
(4) (a) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122. (b) Suzuki, Y.; Ota, S.; Fukuta, Y.; Ueda, Y.; Sato, M. *J. Org. Chem.* **2008**, *73*, 2420. (c) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.
(5) (a) Radziszewski, B. *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1493. (b) Weidenhagen, E. *Ber.* **1935**, *68*, 1953. (c) Weidenhagen, E. *Ber.* **1937**, *70*, 570.
(6) Wang, Z. R. *Comprehensive Organic Name Reactions and Reagents*; Wiley & Sons, Inc., 2010; p 2293.
(7) (a) Steck, E. A.; Day, A. R. *J. Am. Chem. Soc.* **1943**, *65*, 452. (b) Baldwin, J. J.; Christy, M. E.; Denny, G. H.; Habecker, C. N.; Freedman, M. B.; Lyle, P. A.; Ponticello, G. S.; Varga, S. L.; Gross, D. M.; Sweet, C. S. *J. Med. Chem.* **1986**, *29*, 1065. (c) James, D. S.; Fanta, P. E. *J. Org. Chem.* **1963**, *28*, 390. (d) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z. J.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453. (e) Kidwai, M.; Mothsra, P. *Tetrahedron Lett.* **2006**, *47*, 5029. (f) Zuliani, V.; Cocconcelli, G.; Fantini, M.; Ghiron, C.; Rivara, M. *J. Org. Chem.* **2007**, *72*, 4551.
(8) (a) Liu, X.; Wang, D.; Chen, Y. X.; Tang, D.; Chen, B. H. *Adv. Synth. Catal.* **2013**, *355*, 2798. (b) Pusch, S.; Opatz, T. *Org. Lett.* **2014**, *16*, 5430. (c) De Moliner, F.; Hulme, C. *Org. Lett.* **2012**, *14*, 1354.
(9) Chen, C. Y.; Hu, W. P.; Yan, P. C.; Senadi, G. C.; Wang, J. J. *Org. Lett.* **2013**, *15*, 6116.
(10) Rajaguru, K.; Suresh, R.; Mariappan, A.; Muthusubramanian, S.; Bhuvanesh, N. *Org. Lett.* **2014**, *16*, 744.
(11) (a) Huang, H. W.; Ji, X. C.; Wu, W. Q.; Jiang, H. F. *Adv. Synth. Catal.* **2013**, *355*, 170. (b) Cai, Z. J.; Wang, S. Y.; Ji, S. J. *Org. Lett.* **2012**, *14*, 6068.
(12) (a) Gao, Q. H.; Liu, S.; Wu, X.; Wu, A. X. *Org. Lett.* **2014**, *16*, 4582. (b) Gao, Q. H.; Liu, S.; Wu, X.; Zhang, J. J.; Wu, A. X. *J. Org. Chem.* **2015**, *80*, 5984.
(13) Deng, Q. H.; Zou, Y. Q.; Lu, L. Q.; Tang, Z. L.; Chen, J. R.; Xiao, W. J. *Chem. - Asian J.* **2014**, *9*, 2432.
(14) Zhao, M. X.; Zhu, H. K.; Dai, T. L.; Shi, M. *J. Org. Chem.* **2015**, *80*, 11330.
(15) (a) Tang, D.; Guo, X.; Wang, Y.; Wang, J.; Li, J. H.; Huang, Q. W.; Chen, B. H. *Tetrahedron Lett.* **2015**, *56*, 5982. (b) Zhang, J.; Shao, Y.; Wang, H.; Luo, Q.; Chen, J.; Xu, D.; Wan, X. *Org. Lett.* **2014**, *16*, 3312. (c) Xue, W. J.; Li, Q.; Zhu, Y. P.; Wang, J. G.; Wu, A. X. *Chem. Commun.* **2012**, *48*, 3485. (d) Padala, A. K.; Kumar, R. R.; Athimoolam, S.; Ahmed, Q. N. *Org. Lett.* **2016**, *18*, 96. (e) Zhu, Y. L.; Li, C.; Zhang, J. D.; She, M. Y.; Sun, W.; Wan, K. R.; Wang, Y. Q.; Yin, B.; Liu, P.; Li, J. L. *Org. Lett.* **2015**, *17*, 3872. (f) Liu, H.; Duan, T.; Zhang, Z.; Xie, C.; Ma, C. *Org. Lett.* **2015**, *17*, 2932. (g) Zhang, Z.; Xie, C.; Tan, X.; Song, G.; Wen, L.; Gao, H.; Ma, C. *Org. Chem. Front.* **2015**, *2*, 942.
(16) (a) Gao, Q. H.; Wu, X.; Jia, F. C.; Liu, M. C.; Zhu, Y. P.; Cai, Q.; Wu, A. X. *J. Org. Chem.* **2013**, *78*, 2792. (b) Chen, Z. B.; Hong, D.; Wang, Y. G. *J. Org. Chem.* **2009**, *74*, 903. (c) Liu, S.; Chen, R.; Chen, H.; Deng, G.-J. *Tetrahedron Lett.* **2013**, *54*, 3838. (d) Wang, Y.; Zhang, W. X.; Wang, Z. T.; Xi, Z. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8122. (e) Zeng, X.; Ni, Q.; Raabe, G.; Enders, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 2977. (f) Wang, J.; Zhang, X. Z.; Chen, S. Y.; Yu, X. Q. *Tetrahedron* **2014**, *70*, 245.

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Org. Lett. 2016, 18, 1686−1689