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Base-Mediated Regioselective [3+2] Annulation of Ketenimines and Isocyanides: Efficient Synthesis of 1,4,5-Trisubstituted Imidazoles

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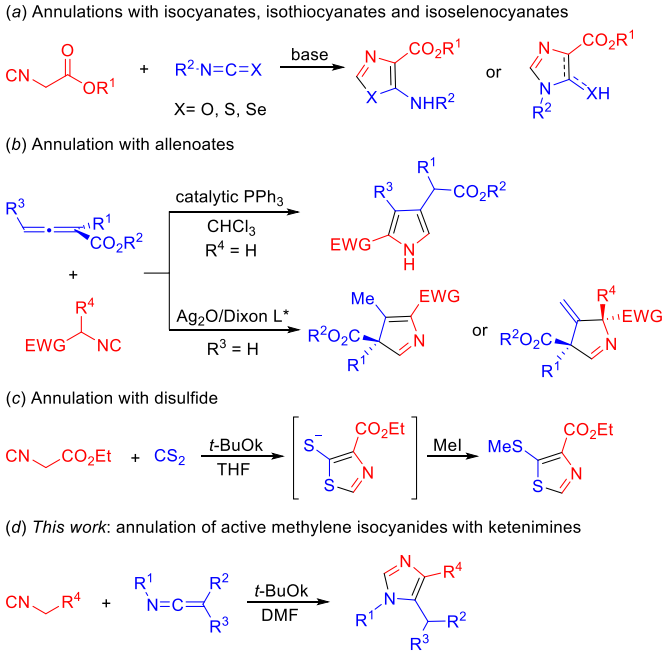
A novel base-mediated regioselective [3+2] annulation of active methylene isocyanides with ketenimines has been developed. In the presence of *t*-BuOK, a wide range of ketenimines readily react with active methylene isocyanides in DMF at 40 °C to afford 1,4,5-trisubstituted imidazoles efficiently.

Isocyanides are versatile and powerful building blocks in the construction of heterocycles.[1] In this context, the active methylene isocyanides are usually viewed as the formal 1,3-dipoles to participate in the annulation with various activated double or triple bonds to produce a wide range of nitrogen-containing five-membered heterocycles.[2] For example, the Van Leusen reaction of active methylene isocyanides with aldehydes or imines has been widely described to form oxazoles and imidazoles.[3] For comparison, however, the annulation of active methylene isocyanides with cumulated double bond to obtain valuable heterocycles has been scarcely investigated. Only a few examples have been reported on the reactions of active methylene isocyanides with isocyanates,[4a] isothiocyanates[4b] and isoselenocyanates[4c] under basic conditions (Scheme 1a). In 2014, Zhao et al. reported a cyclization of allenoates with activated isocyanides for the synthesis of 3*H* or 1*H* pyrroles (Scheme 1b).[5] The annulation of active methylene isocyanides with carbon disulfide also can take place to afford thiazole derivatives (Scheme 1c).[6] Whereas no examples of [3+2] annulation of active methylene isocyanides with ketenimines[7] have been disclosed up to now.[8] The imidazole motif is a key structural unit found in various functional molecules, from naturally occurring bioactive compounds to manmade artificial drugs.[9] Furthermore,



Scheme 1. Annulation of activated methylene isocyanides with cumulated double bond

imidazoles are also widespread in catalysis and coordination chemistry.[10] As a result of this important subunit, a range of methods for the formation of imidazoles have been reported,[11] including the reactions of active methylene isocyanides with carbon-nitrogen multiple bond.[3c,d] Although much progress has been achieved in this area, the development of new methodologies for regioselective synthesis of functionalized imidazoles is still desirable. In this work, we report a novel annulation of active methylene isocyanides with ketenimines[12] for the synthesis of 1,4,5-trisubstituted imidazoles under basic conditions (Scheme 1d).

In the present research, the annulation of ethyl 3-((4-methoxyphenyl)imino)-2-methylacrylate **1a** and ethyl isocyanoacetate **2a** was employed to screen the reaction conditions (Table 1). When **1a** was treated with 1.2 equiv of **2a**,

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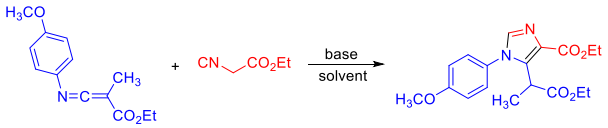
1.0 equiv of NaOH in DMF at room temperature, the desired

Table 1 Optimization of Reaction Conditions[a]



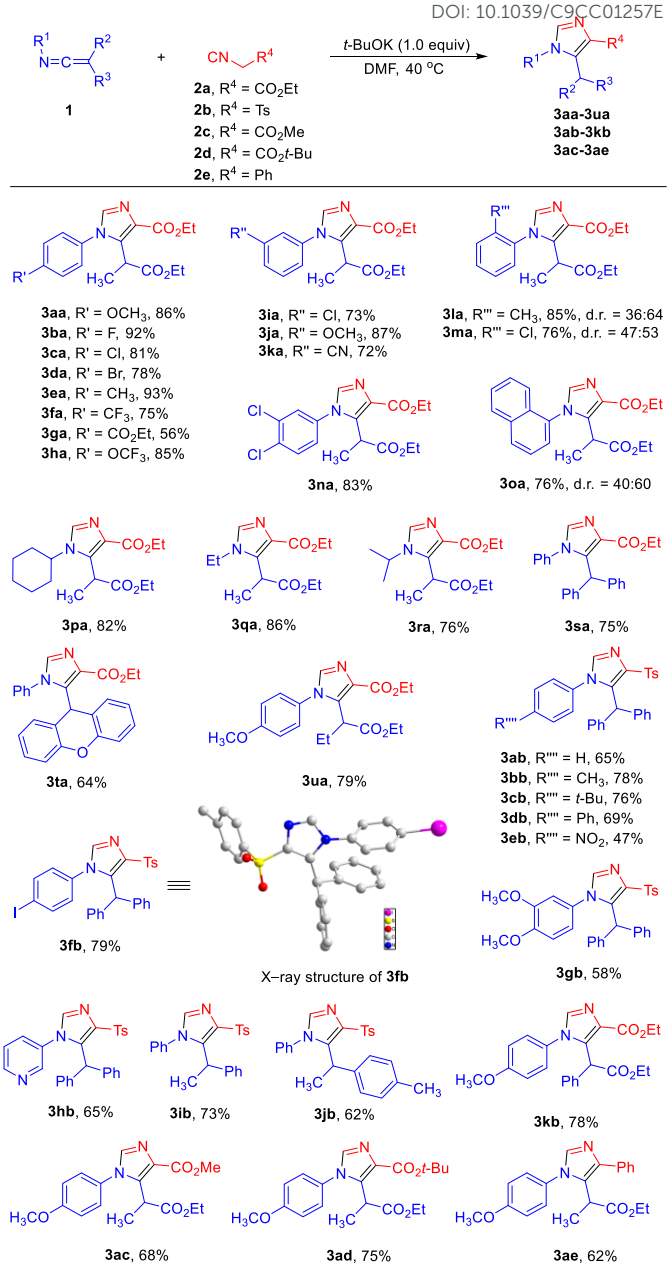
1a 2a 3aa

Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	**3aa** (%)[b]
1	NaOH (1.0)	DMF	rt	0.5	54
2	EtONa (1.0)	DMF	rt	0.5	58
3	*t*-BuONa (1.0)	DMF	rt	0.5	71
4	*t*-BuOK (1.0)	DMF	rt	0.5	83
5	DBU (1.0)	DMF	rt	0.5	43
6	Ag_2CO_3 (1.0)	DMF	rt	12	trace
7	K_2CO_3 (1.0)	DMF	rt	0.5	41
8	Cs_2CO_3 (1.0)	DMF	rt	12	trace
9	*t*-BuOK (1.0)	DCM	rt	12	trace
10	*t*-BuOK (1.0)	1,4-dioxane	rt	0.5	49
11	*t*-BuOK (1.0)	DMSO	rt	0.5	58
12	*t*-BuOK (1.0)	THF	rt	0.5	70
13	*t*-BuOK (1.0)	CH_3OH	rt	12	trace
14	*t*-BuOK (1.0)	C_2H_5OH	rt	12	23
15	*t*-BuOK (1.0)	CH_3CN	rt	0.5	74
16	*t-BuOK (1.0)*	*DMF*	*40*	*0.5*	*86*
17	*t*-BuOK (1.0)	DMF	60	0.5	82
18	*t*-BuOK (1.0)	DMF	80	0.5	77
19	*t*-BuOK (0.5)	DMF	40	0.5	75
20	*t*-BuOK (1.5)	DMF	40	0.5	62
21	-	DMF	40	0.5	0

[a]Reaction conditions, unless otherwise noted: **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.3 mmol), solvent (2.0 mL). [b]Isolated yield.

product **3aa** was obtained in 54% yield (entry 1). For comparison, *t*-BuOK (entry 4) was more effective base than EtONa (entry 2), *t*-BuONa (entry 3), DBU (entry 5), Ag_2CO_3 (entry 6), K_2CO_3 (entry 7), and Cs_2CO_3 (entry 8). We then turned our attention to screen different solvents (entries 9–15). The results indicated that DMF was the best choice (entry 4). Among the reaction temperatures examined, it turned out that the reaction at 40 °C gave the best result (entries 16–18). In addition, it was found that lower product yields of **3aa** were obtained by decreasing or increasing *t*-BuOK loadings (entries 19 and 20). Control experiment verified the requirement of *t*-BuOK (entry 21).

With the optimized conditions in hand, the substrates scope was then investigated. Overall, a number of 1,4,5-trisubstituted imidazoles were successfully prepared with moderate to excellent yields within 0.5 h by the reactions of ethyl isocyanoacetate **2a** or tosylmethylisocyanide **2b** with a wide range of ketenimines **1** (Scheme 2). First, substituents



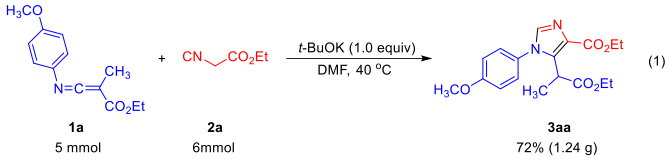
(R^1)

Scheme 2 Synthesis of 1,4,5-trisubstituted imidazoles

on the nitrogen atom of ketenimines were investigated (**3aa**–**3ra**, **3ab**–**3hb**). Aryl substrates **1** with electron-donating groups showed better reactivity than those with electron-withdrawing groups. Various kinds of functional groups, such as OMe, Me, *t*-Bu, NO_2, F, Cl, Br, I, CF_3, OCF_3, CN, CO_2Et, and Ph, were well tolerated. Naphthyl, and pyridyl substrates were also productive, delivering imidazoles in good yields (**3oa** and **3hb**). According to ^1H and ^{13}C NMR spectroscopy data of **3la**, **3ma**, and **3oa**, the diastereoisomers were detected and the diastereomeric ratios were determined by ^1H NMR spectra. Substrates with cyclohexyl, ethyl or isopropyl on the nitrogen atom of ketenimines could be used to generate the corresponding products in good yields (**3pa**–**3ra**). It was

noteworthy that when R^1 was *tert*-butyl substituent, no reaction was observed by TLC monitoring due to, probably, the steric hindrance of the bulky tertiary butyl group. Furthermore, substituents (R^2 and R^3) on the carbon atom of ketenimines were also investigated. When the ketenimines included aryl, methyl, ethyl, CO_2Et, and 9*H*-xanthen-9-yl substituents, the reaction proceeded and gave the desired products **3sa**–**3ua**, **3ib**–**3kb** in good yields. The ester groups of isocyanoacetates were also investigated with the final imidazole products obtained smoothly (**3ac**, **3ad**). Furthermore, it was proved that benzylisocyanide **2e** could also react well with **1a** to give **3ae**. The molecular structure of **3fb** was successfully confirmed by X-ray crystallographic analysis.[13]

To further demonstrate the practical usefulness of the method, a gram-scale reaction was performed with ethyl isocyanoacetate **2a** and ketenimine **1a**. Under the optimized reaction conditions, the reaction could proceed smoothly, affording the desired product **3aa** in 72% yield (eq 1).



(1)

On the above preliminary results, as well as literature precedent, a possible mechanistic pathway is proposed in Scheme 3. Initially, base-mediated deprotonation of ethyl 2-isocyanoacetate **2a** generates the active carbanionic intermediate **A**,[14] which undergoes nucleophilic addition to the central carbon of ketenimine to form intermediate **B**.[7d] Subsequently, a 5-*endo*-*dig* cyclization of **B** takes place to form intermediate **C**,[15] followed by protonation to give intermediate **D**. Finally, isomerization of **D** through 1,3-*H* shift takes place to produce imidazole product **3**. It should be noted that the annulation of active methylene isocyanides with ketenimine only occurs on the C=N double bond of ketenimine with high regioselectivity.[16] The products obtained via intermediate **C'** have not been detected in this transformation.[17] However, a concerted [3+2]-cycloaddition[18] of base-activated **2a** with ketenimines cannot be excluded.

In summary, we have developed a novel base-mediated annulation between active methylene isocyanides and ketenimines for the efficient and straightforward synthesis of 1,4,5-trisubstituted imidazole derivatives. The annulation reaction features broad substrate scope, good functional group compatibility, operational simplicity, and high regioselectivity. Moreover, the present annulation is amenable to gram-scale synthesis. Further studies on the annulation of isocyanides with cumulenes are ongoing in our group.

Scheme 3 The Putative Reaction mechanism

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Notes and references

1 (a) *Isocyanide Chemistry Applications in Synthesis and Materials Science*, ed. V. Nenajdenko, Wiley-VCH, Weinheim, 2012; For reviews on isocyanide, see: (b) A. V. Lygin, and A. de Meijere, *Angew. Chem., Int. Ed.*, 2010, **49**, 9094; (c) M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron, and J. -P. Zhu, *Chem. Soc. Rev.*, 2017, **46**, 1295. For selected examples, see: (d) U. Schöllkopf, and F. Gerhart, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 805; (e) Y. Fang, Z. -L. Zhu, P. Xu, and S. -Y. Wang, *Green Chem.*, 2017, **19**, 1613.

2 (a) J. Liu, Z. Fang, Q. Zhang, Q. Liu, and X. Bi, *Angew. Chem., Int. Ed.*, 2013, **52**, 6953; (b) M. Gao, C. He, H. Chen, R. Bai, B. Cheng, and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 6958; (c) O. V. Larionov, and A. de Meijere, *Angew. Chem., Int. Ed.*, 2005, **44**, 5664; (d) S. Kamijo, C. Kanazawa, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9260; (e) C. Guo, M. -X. Xue, M. -K. Zhu, and L. -Z. Gong, *Angew. Chem., Int. Ed.*, 2008, **47**, 3414; (f) C. Arróniz, A. Gil-González, V. Semak, C. Escolano, J. Bosch, and M. Amat, *Eur. J. Org. Chem.*, 2011, 3755; (g) P. -L. Shao, J. -Y. Liao, Y. -A. Ho, and Y. Zhao, *Angew. Chem., Int. Ed.*, 2014, **53**, 5435; (h) M. Baumann, I. R. Baxendale, S. V. Ley, C. D. Smith, and G. K. Tranmer, *Org. Lett.*, 2006, **8**, 5231; (i) F. Sladojevich, A. Trabocchi, A. Guarna, and D. J. Dixon, *J. Am. Chem. Soc.*, 2011, **133**, 1710; (j) H. Y. Kim, and K. Oh, *Org. Lett.*, 2011, **13**, 1306; (k) C. Kanazawa, S. Kamijo, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 10662; (l) J. Aydin, K. S. Kumar, L. Eriksson, and K. J. Szabó, *Adv. Synth. Catal.*, 2007, **349**, 2585.

3 (a) A. M. van Leusen, J. Wildeman, and O. H. Oldenzeil, *J. Org. Chem.*, 1977, **42**, 1153; (b) A. M. van Leusen, *Lect. Heterocycl. Chem.*, 1980, **5**, S-111; (c) V. Gracias, A. F. Gasiecki, and S. W. Djuric, *Org. Lett.*, 2005, **7**, 3183; (d) G. S. M. Sundaram, B. Singh, C. Venkatesh, H. Ila, and H. Junjappa, *J. Org. Chem.*, 2007, **72**, 5020; (e) R. Schröder, U. Schöllkopf, E. Blume and I. Hoppe, *Liebigs Ann. Chem.*, 1975, 533.

4 (a) D. M. Solomon, R. K. Rizvi, and J. J. Kaminski, *Heterocycles*, 1987, **26**, 651; (b) M. Suzuki, T. Moriya, K. Matsumoto, and M. Miyoshi, *Synthesis*, 1982, 874; (c) H. Maeda, N. Kambe, N. Sonoda, S. Fujiwara, and T. Shinike, *Tetrahedron*, 1997, **40**, 13667.

5 J. -Y. Liao, P. -L. Shao, and Y. Zhao, *J. Am. Chem. Soc.*, 2015, **137**, 628.

6 U. Schollkopf, P. Porsch, and E. Blume, *Liebigs Ann. Chem.*, 1976, **11**, 2122.

7 For reviews on ketenimines, see: (a) P. Lu, and Y. -G. Wang, *Chem. Soc. Rev.*, 2012, **41**, 5687; (b) R. H. Dodd,

and K. Cariou, *Chem. – Eur. J.,* 2018, **24**, 2297; (c) M. Alajarin, M. Marin-Luna, and A. Vidal, *Eur. J. Org. Chem.,* 2012, **2012**, 5637; (d) P. Lu, and Y. G. Wang, *Synlett,* 2010, 165.

8 Reactions of isocyanides with ketenimines: (a) J. Ruiz, M. P. Gonzalo, M. Vivanco, M. R. Diazb, and S. Garcia-Grandab, *Chem. Commun.,* 2011, **47**, 4270; (b) L. Capuano, P. Morsdorf, and H. Scheidt, *Chem. Ber.,* 1983, **116**, 741; (c) L. Capuano, R. Dahm, V. Port, R. Schnur, and V. Schramm, *Chem. Ber.,* 1988, **121**, 271.

9 (a) V. G. Silva, R. O. Silva, S. R. B. Damasceno, N. S. Carvalho, R. S. Prudêncio, K. S. Aragão, M. A. Guimarães, S. A. Campos, L. M. C. Véras, M. Godejohann, J. R. S. A. Leite, A. L. R. Barbosa, and J. V. R. Medeiros, *J. Nat. Prod.,* 2013, **76**, 1071; (b) J. Muñoz, and M. Köck, *J. Nat. Prod.,* 2016, **79**, 434; (c) L. De Luca, *Curr. Med. Chem.,* 2006, **13**, 1; (d) L. Zhang, X. -M. Peng, G. L. V. Damu, R. -X. Geng, and C. -H. Zhou, *Med. Res. Rev.,* 2014, **34**, 340.

10 (a) W. A. Herrmann, *Angew. Chem., Int. Ed.,* 2002, **41**, 1290; (b) T. R. Jensen, C. P. Schaller, M. A. Hillmyer, and W. B. Tolman, *J. Organomet. Chem.,* 2005, **690**, 5881; (c) M. Poyatos, J. A. Mata, and E. Peris, *Chem. Rev.,* 2009, **109**, 3677; (d) M. C. Leclerc, S. I. Gorelsky, B. M. Gabidullin, I. Korobkov, and R. T. Baker, *Chem. – Eur. J.,* 2016, **22**, 8063; (e) A. Levens, F. An, M. Breugst, H. Mayr, and D. W. Lupton, *Org. Lett.,* 2016, **18**, 3566.

11 For review, see: S. Kamijo, and Y. Yamamoto, *Chem. – Asian J.,* 2007, **2**, 568; For examples on the synthesis of imidazoles from isocyanides, see: (a) X. -S. Huang, X. -F. Cong, P. -B. Mi, and X. -H. Bi, *Chem. Commun.,* 2017, **53**, 3858; (b) J. -J. Zhang, Q. -H. Gao, X. Wu, X. Geng, Y. -D. Wu, and A. -X. Wu, *Org. Lett.,* 2016, **18**, 1686; (c) B. Pooi, J. Lee, K. Choi, H. Hirao, and S. -H. Hong, *J. Org. Chem.,* 2014, **79**, 9231; (d) C. Kanazawa, S. Kamijo, and Y. Yamamoto, *J. Am. Chem. Soc.,* 2006, **128**, 10662; (e) R. Bossio, S. Marcaccini, and R. Pepino, *J. Org. Chem.,* 1996, **61**, 2202; (f) R. Aumann, and H. Heinen, *Chem. Ber.,* 1989, **122**, 1139.

12 (a) W. W. Barker, and J. H. Gardner, *J. Heterocycl. Chem.,* 1969, **6**, 251; (b) W. J. Kauffman, *J. Org. Chem.,* 1970, **35**, 4244; (c) N. Murai, M. Komatsu, Y. Ohshiro, and T. Agawa, *J. Org. Chem.,* 1977, **42**, 448; (d) W. W. Barker, and W. E. McHenry, *J. Org. Chem.,* 1979, **44**, 1175; (e) T. Aoyama, S. Katsuta, and T. Shioiri, *Heterocycles,* 1989, **28**, 123; (f) A. Toyohiko, N. Takao, M. Kiyotaka, U. Yuka, and S. Takayuki, *Synthesis,* 1991, 1163; (g) H. Maas, C. Bensimon, and H. Alper, *J. Org. Chem.,* 1998, **63**, 17; (h) C. Larksarp, O. Sellier, and H. Alper, *J. Org. Chem.,* 2001, **66**, 3502; (i) H. Giera, R. Huisgen, and K. Polborn, *Eur. J. Org. Chem.,* 2005, **2005**, 3781; (j) Y. Cheng, Y. -G. Ma, X. -R. Wang, and J. -M. Mo, *J. Org. Chem.,* 2009, **74**, 850; (k) J. -M. Mo, Y. -G. Ma, and Y. Cheng, *Org. Biomol. Chem.,* 2009, **7**, 5010.

13 Crystallographic data for **3fb** are available as Supporting Information or as CCDC-1887245. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

14 A. Bhattacharyya, C. K. Shahi, S. Pradhan, and M. K. Ghorai, *Org. Lett.,* 2018, **20**, 2925.

15 D. Monge, K. L. Jensen, I. Marin, and K. A. Jørgensen, *Org. Lett.,* 2011, **13**, 328.

16 The annulation of ketenimines with dual functional reagents occurred only on the C=C double bond of ketenimines, see: (a) S. -L. Cui, J. Wang, and Y. -G. Wang, *Tetrahedron,* 2008, **64**, 487; (b) S. -L. Cui, J. Wang, and Y. -G. Wang, *Org. Lett.,* 2007, **9**, 5023.

17 For a cyclization of in situ generated ketenimines with (*p*-toluenesulfonyl)methyl isocyanide occurred only on the C=C double bond of ketenimines to afford pyrroles, see: I. Yavari and M. Nematpour, *Helv. Chim. Acta,* 2013, **96**, 2098.

18 (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, ed. A. Padwa, W. H. Pearson, John Wiley & Sons, New York, 2002. (b) K. V. Gothelf, and K. A. Jørgensen, *Chem. Rev.,* 1998, **98**, 863; (c) M. Kissane, and A. R. Maguire, *Chem. Soc. Rev.,* 2010, **39**, 845; (d) F. Heaney, *Eur. J. Org. Chem.,* 2012, **2012**, 3043; (e) S. Roscales, and J. Plumet, *Org. Biomol. Chem.,* 2018, **16**, 8446.

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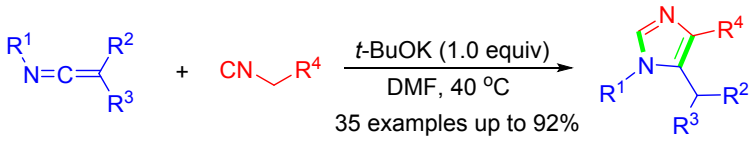
DOI: 10.1039/C9CC01257E



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