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Remote Directed Isocyanation of Unactivated C(sp^3)−H Bonds: Forging Seven-Membered Cyclic Ureas Enabled by Copper Catalysis

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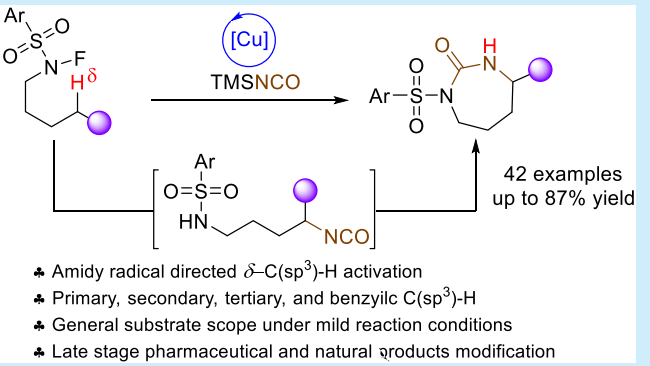
ABSTRACT: Reported herein is an unprecedented copper-catalyzed site-selective δ-C(sp^3)−H bonds activation of aliphatic sulfonamides for constructing the synthetically useful seven-membered *N*-heterocycles. A key to success is the use of in-situ-formed amide radicals, to activate the inert C(sp^3)−H bond, and inexpensive TMSNCO, as a coupling reagent under mild conditions. To the best of our knowledge, this represents the first use of alkylamine derivatives as a five-membered synthon to prepare a seven-membered *N*-heterocycles.



Medium-ring nitrogen heterocycles exhibit a wide range of pharmaceutical activities, and they have found a myriad of applications.[1] Among them, the seven-membered cyclic urea scaffold is the core motif in a family of bioactive agents, such as highly potent HIV protease inhibitors, including structurally symmetrical **DMP 323** and **DMP 450**, and the unsymmetrical yet intriguing β-lactamase inhibitor **NXL-104** (see Figure 1).[2] Besides, it also appears in natural

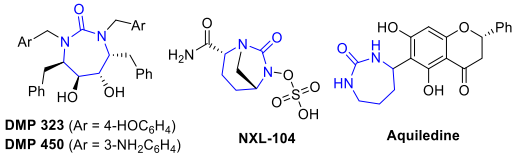


Figure 1. Selected bioactive and natural compounds containing seven-membered cyclic urea.

products, such as aquiledine.[3] As a consequence, developing efficient and selective process for the assembly of such skeleton has been a long-standing pursuit for synthetic chemists.

However, probably due to the unfavorable entropic and/or enthalpic factors associated with medium-ring synthesis,[4] methods to construct such seven-membered cyclic urea compounds are sparsely disclosed with limited catalytic versions.[5] By manipulating highly functionalized substrates, several Pd-catalyzed[5a] and Ru-catalyzed[5b] intramolecular strategies were disclosed. In sharp contrast, transition-metal-catalyzed intermolecular strategies are rather limited (Figure 2). For instance, McElwee-White and co-workers[5c] developed W-catalyzed carbonylation of symmetric diamine under 80 atm of toxic CO atmosphere (see Figure 2a, left). The Bower

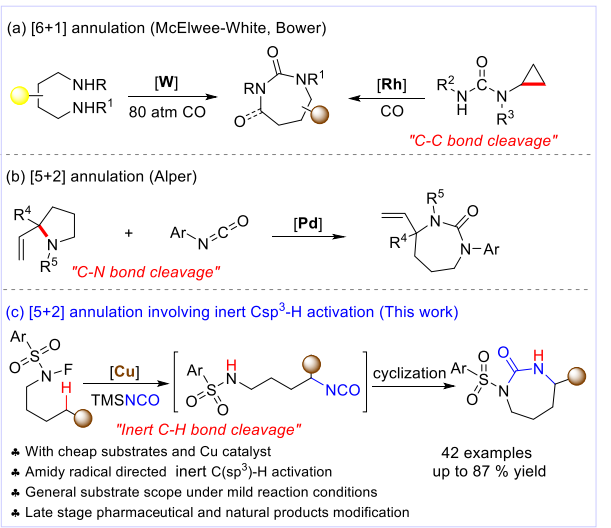


Figure 2. Catalytic intermolecular strategies for preparing seven-membered cyclic urea.

group[5d] reported one elegant example via Rh-catalyzed carbonylative heterocyclization of cyclopropyl urea (Figure 2a, right). Alper[5e] reported the Pd-catalyzed [5 + 2] cycloaddition between 2-vinylpyrrolidines and aryl isocyanates

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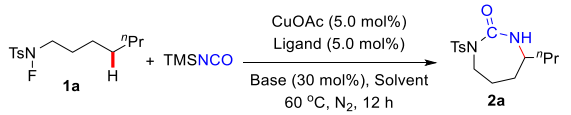
to get the seven-membered urea (Figure 2b). However, these catalytic methods often suffer from the need of cumbersome steps to prepare the highly functionalized materials, the use of expensive metal catalysts to cleave the polarized C−C or C−N bond, toxic reagents, or harsh conditions with low efficiency. Consequently, it is still highly desirable to develop novel practical methods for the facile synthesis of seven-membered urea.

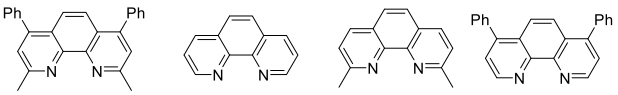
On the other hand, the Hofmann−Löffler−Freytag (HLF)[6] reaction constitutes a key breakthrough via nitrogen-centered radicals triggered a 1,*n*-hydrogen atom transfer (HAT) process during the activation of inert C(sp^3)−H bonds for versatile transformations, including the formation of nitrogen heterocycles. Over a century, some elegant examples for preparing five-[7] and six-membered[8] nitrogen heterocycles have been disclosed. However, since the 1,5-HAT is kinetically more favored,[9] the construction of seven-membered ones is still challenging and remains largely unexplored. In view of this, coupled with recent discovery from several groups[10] and us[11] that Cu(I) could easily reduce *N*-fluoro-tosylamide, to form the key amidyl radical, we envisioned that this strategy can make the *N*-fluoro-tosylamide as a five-membered synthon, since the selective 1,5-HAT process will generate the carbon radicals that is located in the *δ*-position relative to the amide group. Furthermore, by trapping the radical with a suitable two-membered synthon such as an isocyanate group, selective isocyanation might occur, and subsequent intramolecular nucleophilic addition will provide a new alternative for getting the seven-membered nitrogen heterocycles. While conceptually feasible, to get such site-selective isocyanation of inert C(sp^3)−H bond is nontrivial, and it faces several difficulties. First, the super reactivity of the isocyanate group might make it difficult to be compatible with the reaction conditions.[12] Second, Muñiz and co-workers have reported that such substrates may easily undergo intramolecular cyclization to form five- or six-membered *N*-cycles under Cu(I) catalysis.[8d] Third, the plausible fluorination via trapping the carbon radical with another N−F substrate also should be avoided.[13] Herein, we wish to report an unprecedented protocol for the facile preparation of seven-membered cyclic urea by coupling the readily available N−F sulfonamide with inexpensive TMSNCO, using Cu catalysis (Figure 2c). By successfully overcoming these aforementioned competitive side reactions, our method allows one to synthesize seven-membered cyclic urea under mild conditions with good functional group tolerance and high regioselectivity.

We commenced the optimal condition screen by using 5 mol % CuOAc, *N*-fluoro-tosylamide (**1a**, 0.20 mmol) and inexpensive TMSCNO (1.5 equiv) as the isocyanation source, with absolute MeCN as the solvent and the reaction was operating at 60 °C for 12 h under a N_2 atmosphere (for full details, please see the Supporting Information, as well as Table 1). While no desired product was observed without ligand, adding 5 mol % of 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline (BC), to our delight, enabled the isolation of anticipated **2a** with 20% yield (Table 1, entries 1 and 2). Considering that the base might be helpful to enhance the nucleophilicity of sulfonamide, NaOAc was tested and it turns out that adding 0.3 equiv could improve the yield to 53% (Table 1, entry 3). Encouraged by this, a systematic screening of copper salts bearing different anions showed that CuOAc was the best choice (not shown in Table 1). Screening other commercially available ligands indicated that the use of neocuproine (NC) as a ligand could deliver **2a** with 61% yield (Table 1, entries 5−7). Further optimization of reaction solvents indicated that EtOAc is best for this transformation and the yield can reach 67% (Table 1, entries 8−11). In order to further increase the efficiency, other bases, such as LiOAc, K_2CO_3, HCOONa, EtONa, and ^{t}BuONa, were also checked, with LiOAc exhibiting the best yield (74%) (see Table 1, entries 13−16). Inferior yield was observed by either elevating or decreasing the reaction temperature (see Table 1, entries 17 and 18).

Table 1. Optimization of the C(sp^3)−H Activation for Preparing Seven-Membered Cyclic Urea[a]



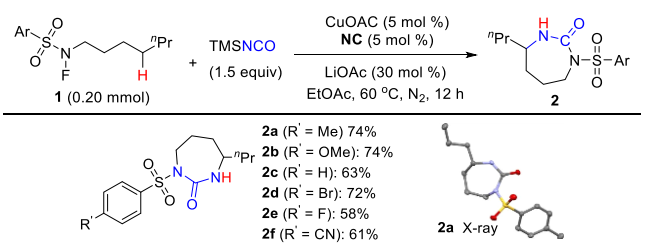
entry	ligand	base	solvent	yield[b] (%)
1[c]	–	–	MeCN	0
2	**BC**	–	MeCN	20
3	**BC**	NaOAc	MeCN	58
4	**BC**	NaOAc	MeCN	53
5	**NC**	NaOAc	MeCN	61
6	**Phen**	NaOAc	MeCN	22
7	**L1**	NaOAc	MeCN	42
8	**NC**	NaOAc	DCM	60
9	**NC**	NaOAc	DCE	57
10	**NC**	NaOAc	1,4-dioxane	48
11	**NC**	NaOAc	EtOAc	67
12	**NC**	HCOONa	EtOAc	57
13	**NC**	EtONa	EtOAc	61
14	**NC**	^{t}BuONa	EtOAc	56
15	**NC**	K_2CO_3	EtOAc	69
16	**NC**	**LiOAc**	**EtOAc**	**74**
17[d]	**NC**	NaOAc	EtOAc	63
18[e]	**NC**	NaOAc	EtOAc	0



[a]Reactions were performed with **1a** (0.2 mmol), in 2 mL of solvent under a N_2 atmosphere, unless noted otherwise. [b]Isolated yield. [c]The reaction was performed for 24 h. [d]Under 80 °C. [e]Under 25 °C.

The scope of the sulfonamide protecting groups was examined first, and these results are summarized in Scheme 1. Arylsulfonamides bearing both electron-donating and electron-withdrawing electronic properties provided moderate to good yields of corresponding seven-membered cyclic urea **2a**−**2f** (58%−74%), and the efficiency of these with electron-donating groups is better than that of electron-withdrawing ones. The configuration of compound **2a** was unambiguously established by single-crystal X-ray analyses.

Scheme 1. Scope of Sulfonamide



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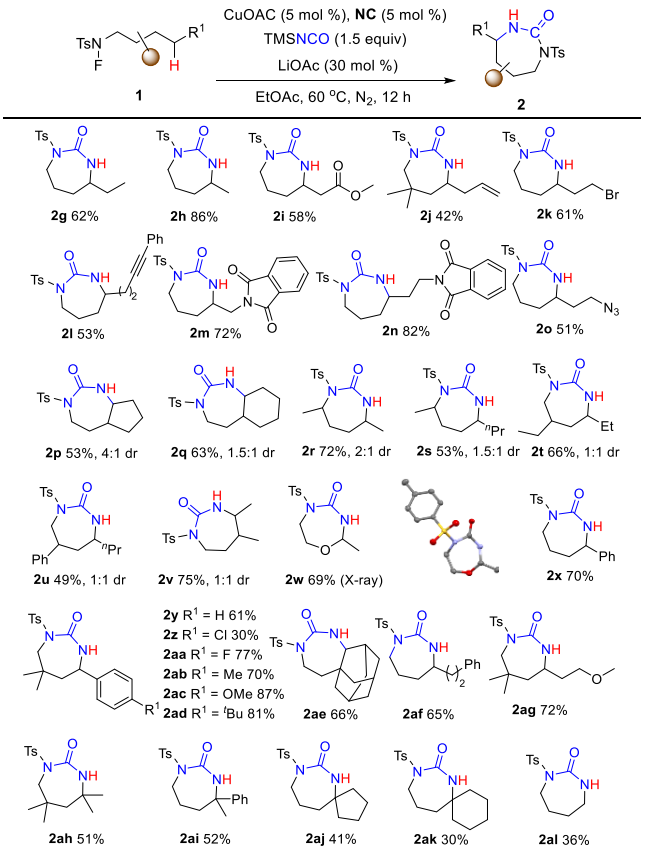
Next, under the optimal conditions, the alkyl substituent scope of the reaction was examined; these results are summarized in Scheme 2. The reaction of TMSNCO with

Scheme 2. Scope of the C(sp^3)−H Activation for Preparing Seven-Membered Cyclic Urea[a]



[a]Reactions were performed using **1** (0.2 mmol), TMSNCO (1.5 equiv), CuOAc (0.05 equiv), **NC** (0.05 equiv), LiOAc (0.3 equiv), and 2 Ml absolute ethyl acetate at 60 °C under a N_2 atmosphere for 12 h (TLC analysis indicated the full conversion of **1**), unless otherwise stated. Values shown beside compound identifications represent the yield of the isolated product.

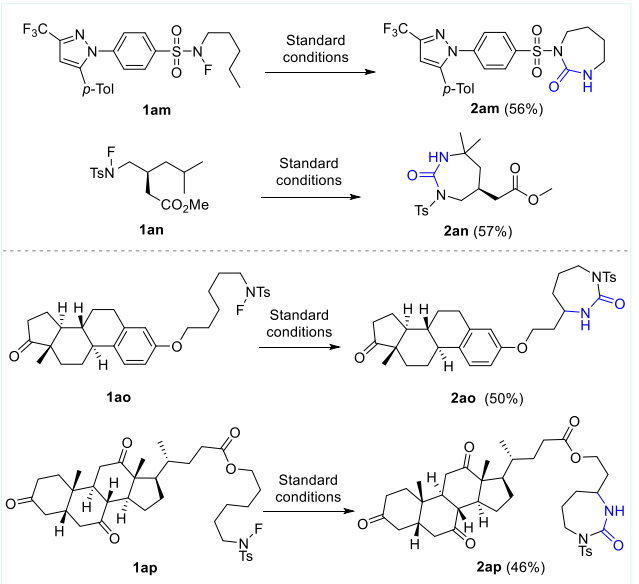
various *N*-fluoro-tosylamide derivatives afforded the desired seven-membered cyclic ureas **2** in 30%−87% yields. For secondary alkyl-substituted inert C−H bonds, amination occurred with complete regioselectivity and could be converted to the desired seven-membered cyclic urea (**2g**, **2h**) in 62% and 86%, respectively.

The reaction has very good functional group compatibility. For example, substrates **1i**−**1o**, which contain ester, alkenyl, alkynyl, bromo, amide, and azido groups, also worked well in the reaction, affording the desired cyclic urea (**2i**−**2o**) in good yields (42%−82%). These functional groups provide the opportunity for further modification. In order to examine the stereoselectivity of this method, some nonactivated, simple cyclohexyl and cyclopentyl groups were first tested; we could get paracyclic products **2p** (53%, diastereomeric ratio (dr) = 4:1), and **2q** (63%, dr = 1.5:1) in good yields, albeit with moderate diastereoselectivity. Next, open-chain substrates having 1,4-, 1,3-, and 1,2-stereoinductive effects, such as **1r**, **1s**, **1t**, **1u**, and **1v**, were tested, and the corresponding cyclic urea products (**2r**, **2s**, **2t**, **2u**, and **2v**) could be obtained in yields of 49%−75%, albeit with low stereoselectivity.

As expected, remote C(sp^3)−H isocyanation and tandem cyclization beside an O atom was also achieved, to provide the oxa-seven-membered cyclic urea product **2w** (69%). Moreover, the structure of **2w** was unambiguously established by single crystal X-ray analyses. Besides, substrates bearing benzylic C−H bonds could also deliver the products **2x**−**2ad** smoothly in moderate to good yield (30%−87%). Notably, these cyclic ureas are very similar to some diazepanone derivatives or analogues, which were used as 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) inhibitors.[14] Furthermore, we could use a convenient approach to remove the Ts group of the cyclic urea product **2y** to obtain the corresponding free urea. (For details, please see the Supporting Information.) In a ternary competition between δ/ε secondary C−H bonds and a ζ benzylic C−H bond, only the product of 1,5-HAT was observed **2af** (65%). For a congener substrate in which the ζ-position had a methoxy substituent, only the 1,5-HAT product **2ag** (72%) was obtained. The reaction also worked with tertiary inert C−H bonds, such that **1ah** could give the corresponding product **2ah** in medium yield (51%). The tertiary benzylic position C−H bonds also provide the corresponding cyclic urea product **2ai** in 52% yield. For the five- and six-membered cyclic systems such **1aj** and **1ak**, the corresponding cyclic urea products **2aj** and **2ak** were isolated with low yields of 41% and 30%, respectively. To our delight, the *unactivated primary* C−H bonds also participated well in the reaction, affording the cyclic urea product **2al** (36%).

To further demonstrate the functional-group compatibility and the potential application of this methodology, late-stage functionalization of both medicinal and natural product derivatives was examined under standard reaction conditions, and these results are summarized in Scheme 3. The reaction of celecoxib- and pregabalin-derived substrates **1am** and **1an** worked well under the standard conditions, delivering the corresponding cyclic urea products **2am** and **2an** in moderate yields. In addition, natural product derivatives **1ao** (from

Scheme 3. Late-Stage Functionalization of Medicine Derivatives and Natural Product Derivatives



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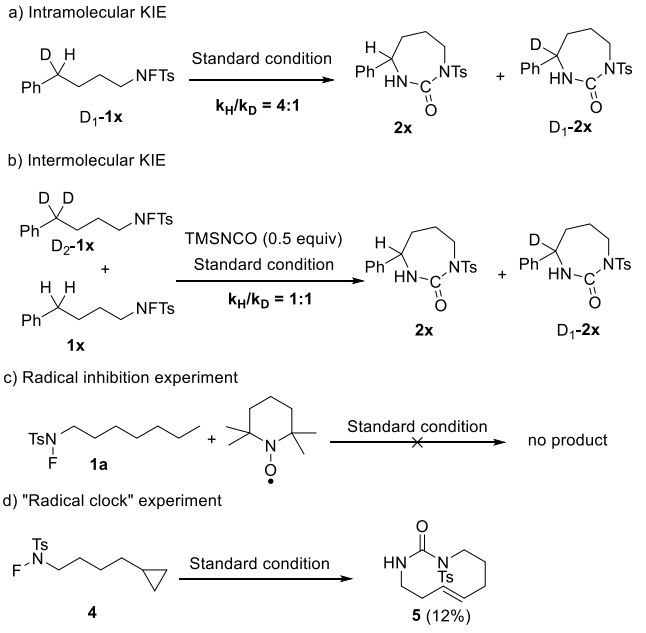
estrone) and **1ap** (from dehydrocholic acid), can also give the desired cyclic urea products **2ao** and **2ap** in 50% and 46% yields, respectively.

In order to shed light on the mechanism, a series of control experiments was conducted (Scheme 4). First, the reaction of

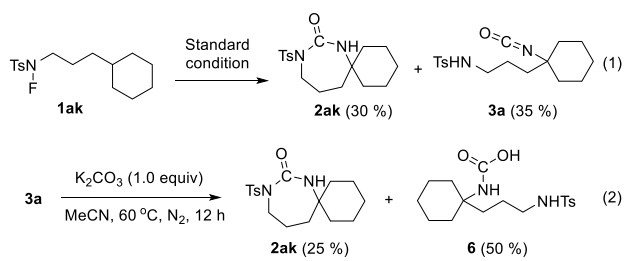
Scheme 4. Mechanistic Investigation



[D_1]-**1x** with TMSCNO under standard reaction conditions afforded [D_1]-**2x**/**2x** in a ratio of 4:1, indicating an intramolecular KIE value of 4:1 (Scheme 4a). A side-by-side kinetic experiment using **1x** and [D_2]-**1x** provided an intermolecular KIE value of 1:1 (Scheme 4b). These data indicated that the 1,5-HAT, which represents an off-catalytic cycle process, contributed only minimally to the overall reaction rate.[15] Second, δ-C(sp^3)−H activation was completely inhibited in the presence of 1.5 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (Scheme 4c), indicating that the reaction might work through a radical mechanism. Furthermore, "radical clock" experiment with cyclopropane **4** delivered the ring-opened product **5** (Scheme 4d), indicating that an intramolecular 1,5-HAT process might be involved.

Moreover, while performing the reaction of **1ak** with TMSNCO under standard conditions, we could isolate the key proposed alkyl isocyanate **3a** with 35% yield (see eq 1 in Scheme 5). Furthermore, it is identified that this alkyl isocyanate **3a** could be transformed to the desired **2ak** with 25% yield, under base condition cyclization (see eq 2 in Scheme 5). This result indicated that the reaction might

Scheme 5. Characterization of Key Isocyanate Intermediates



undergo C(sp^3)−H isocyanation to generate alkyl isocyanate **3** at first; subsequently, intramolecular nucleophilic cyclization to form cyclic urea will happen smoothly, with the assistance of a base.

Based on these preliminary studies, a plausible mechanism was proposed (Figure 3). Initially, reduction of *N*-fluoro-

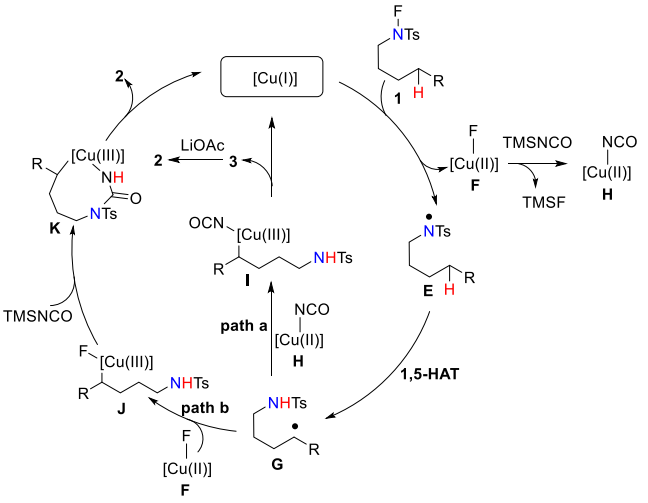


Figure 3. Proposed mechanism.

tosylamide **1** by a ligand coordinated [Cu(I)] via a single-electron-transfer mechanism produced F[Cu(II)] **F** and amidyl radical **E**. Subsequently, amidyl radical **E** underwent intramolecular 1,5-HAT to afford the carbon-centered radical **G**. The strong affinity[16] of F and Si would promote ligand transfer of F[Cu(II)] with TMSNCO, delivering intermediate **H**. Upon radical rebound with **G**, OCN-[Cu(III)]R species **I** could be formed,[17] and the following reductive elimination would produce the remote C(sp^3)−H isocyanation product **3** with concurrent regeneration of the catalytic Cu(I) species ("path a" in Figure 3). Noteworthy, the isocyanate group transfer step was confirmed by density functional theory (DFT) calculation, indicating that a lower energy was needed for the process involving Cu(III) intermediate **I** than that needed for direct radical substitution to the isocyanate in **H**.[18] (For details, please see Figure S1 in the Supporting Information.) Finally, **3** underwent cyclization to form cyclic urea **2** with the assistance of LiOAc.[19] Alternatively, **G** might also be trapped by **F**, forming intermediate **J** at first. Subsequent trapping of TMSNCO with the amide group of **G** enables the generation of **K**, and the final reductive elimination will give rise to **2** and Cu(I) ("path b" in Figure 3).

In summary, we report an unprecedented copper-catalyzed site-selective δ-C(sp^3)−H bonds activation of aliphatic sulfonamides for constructing the synthetically innate, and difficult yet very useful seven-membered *N*-heterocycles for the first time, enabling the preparation of versatile seven-membered urea under mild reaction conditions. This also represents the first construction of seven-membered *N*-heterocycles using the 1,5-HAT process of the Hofmann−Löffler−Freytag reaction, and this can be used for the late-stage functionalization of pharmaceutical and natural product derivatives. Applying the current strategy to asymmetric versions is ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04542.

Details of experimental procedures; ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1958759 and 1958760 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews and examples, see: (a) Garg, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C. *Chem. Rev.* **1999**, *99*, 3525−3621. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3008. (c) Majumdar, K. C. *RSC Adv.* **2011**, *1*, 1152−1170. (d) Avram, S.; Bologa, C.; Flonta, M. L. *J. Mol. Model.* **2005**, *11*, 105−115. (e) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257−10274.

(2) (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; et al. *Science* **1994**, *263*, 380−384. (b) De Lucca, G. V.; Lam, P. Y. S. *Drugs Future* **1998**, *23*, 987−994. (c) Ehmann, D. E.; Jahic, H.; Ross, P. L.; Gu, R. F.; Hu, J.; Kern, G.; Walkup, G. K.; Fisher, S. L. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 11663−11668.

(3) Chen, S. B.; Gao, G. Y.; Leung, H. W.; Yeung, H. W.; Yang, J. S.; Xiao, P. G. *J. Nat. Prod.* **2001**, *64*, 85−87.

(4) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(5) (a) Hayashi, M.; Sai, H.; Horikawa, H. *Heterocycles* **1998**, *48*, 1331−1335. (b) Kim, M.; Gajulapati, K.; Kim, C.; Jung, H. Y.; Goo, J.; Lee, K.; Kaur, N.; Kang, H. J.; Chung, S. J.; Choi, Y. *Chem. Commun.* **2012**, *48*, 11443−11445. (c) Hylton, K.-G.; Main, A. D.; McElwee-White, L. *J. Org. Chem.* **2003**, *68*, 1615−1617. (d) McCreanor, N. G.; Stanton, S.; Bower, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 11465−11468. (e) Zhou, H.-B.; Alper, H. *J. Org. Chem.* **2003**, *68*, 3439−3445.

(6) (a) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558−560. (b) Löffler, K.; Freytag, C. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427−3431. For selected reviews, see: (c) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55−64. (d) Neale, R. S. *Synthesis* **1971**, *1971*, 1−15. (e) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657−1668. (f) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337−350.

(7) For selected recent developments, see: (a) Martín, A.; Pérez-Martín, I.; Suárez, E. *Org. Lett.* **2005**, *7*, 2027−2030. (b) Fan, R.; Pu, D.; Wen, F.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8994−8997. (c) Yang, M.; Su, B.; Wang, Y.; Chen, K.; Jiang, X.; Zhang, Y.-F.; Zhang, X.-S.; Chen, G.; Cheng, Y.; Cao, Z.; Guo, Q.-Y.; Wang, L.; Shi, Z.-J. *Nat. Commun.* **2014**, *5*, 4707. (d) Martínez, C.; Muñiz, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 8287−8291. (e) Wappes, E. A.; Fosu, S. C.; Chopko, T. C.; Nagib, D. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 9974−9978. (f) Meng, D.; Tang, Y.; Wei, J.; Shi, X.; Yang, M. *Chem. Commun.* **2017**, *53*, 5744−5747. (g) Becker, P.; Duhamel, T.; Martínez, C.; Muñiz, K. *Angew. Chem., Int. Ed.* **2018**, *57*, 5166−5170. (h) Duhamel, T.; Stein, C. J.; Martínez, C.; Reiher, M.; Muñiz, K. *ACS Catal.* **2018**, *8*, 3918−3925.

(8) (a) Wawzonek, S.; Nelson, M. F., Jr.; Thelen, P. J. *J. Am. Chem. Soc.* **1951**, *73*, 2806−2808. (b) Freire, R.; Martín, A.; Pérez-Martín, I.; Suárez, E. *Tetrahedron Lett.* **2002**, *43*, 5113−5116. (c) Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 12592−12595. (d) Bafaluy, D.; Muñoz-Molina, J. M.; Funes-Ardoiz, I.; Herold, S.; de Aguirre, A. J.; Zhang, H.; Maseras, F.; Belderrain, T. R.; Pérez, P. J.; Muñiz, K. *Angew. Chem., Int. Ed.* **2019**, *58*, 8912−8916.

(9) Nechab, M.; Mondal, S.; Bertrand, M. P. *Chem. - Eur. J.* **2014**, *20*, 16034−16059 and references cited therein..

(10) (a) Li, Z.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 13288−13292. (b) Zhang, Z.; Stateman, L. M.; Nagib, D. A. *Chem. Sci.* **2019**, *10*, 1207−1211. (c) Liu, Z.; Xiao, H.; Zhang, B.; Shen, H.; Zhu, L.; Li, C. *Angew. Chem., Int. Ed.* **2019**, *58*, 2510−2513. (d) Yin, Z.; Zhang, Y.; Zhang, S.; Wu, X.-F. *J. Catal.* **2019**, *377*, 507−510. (e) Zhang, Z.; Zhang, X.; Nagib, D. A. *Chem* **2019**, *5*, 3127−3134. (f) Modak, A.; Pinter, E. N.; Cook, S. P. *J. Am. Chem. Soc.* **2019**, *141*, 18405.

(11) Zhang, H.; Zhou, Y.; Tian, P.; Jiang, C. *Org. Lett.* **2019**, *21*, 1921−1925.

(12) (a) Saunders, J. H.; Slocombe, R. J. *Chem. Rev.* **1948**, *43*, 203−218. (b) Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927−1945. (c) Allen, A. D.; Tidwell, T. T. *Chem. Rev.* **2013**, *113*, 7287−7342. For the first radical isocyanation of $C(sp^3)$−H bonds, please see: (d) Huang, X.; Zhuang, T.; Kates, P. A.; Gao, H.; Chen, X.; Groves, J. T. *J. Am. Chem. Soc.* **2017**, *139*, 15407−15413.

(13) (a) Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3570−3572. (b) Rueda-Becerril, M.; Chatalova Sazepin, C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J.*

Am. Chem. Soc. **2012**, *134*, 4026−4029. (c) Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 11079−11083.
(14) (a) Claremon, D. A.; Zhuang, L.; Tice, C. M.; Singh, S. B.; Ye, Y.; Zhao, W.; Leftheris, K. U.S. Patent 20100041637 A1, Feb. 18, 2010. (b) Claremon, D. A.; Zhuang, L.; Ye, Y.; Singh, S. B.; Tice, C. M. PCT International Application, WO 2009102428 A2, Aug. 20, 2009.
(15) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072.
(16) (a) Wu, J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2000**, *65*, 1344−1348. (b) Poisson, T.; Dalla, V.; Marsais, F.; Dupas, G.; Oudeyer, S.; Levacher, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7090−7093. (c) Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 2529−2533.
(17) (a) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 10202−10205. (b) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2016**, *138*, 15547−15550. (c) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. *Science* **2016**, *353*, 1014−1018. (d) Wang, F.; Chen, P.; Liu, G. *Acc. Chem. Res.* **2018**, *51*, 2036−2046.
(18) Although the direct isocyanate group transfer in **H** to form the product **3** cannot be completely excluded at the current stage, for examples, please see: (a) Liu, Z.; Chen, H.; Lv, Y.; Tan, X.; Shen, H.; Yu, H.-Z.; Li, C. *J. Am. Chem. Soc.* **2018**, *140*, 6169−6175. (b) Xiao, H.; Shen, H.; Zhu, L.; Li, C. *J. Am. Chem. Soc.* **2019**, *141*, 11440−11445. (c) Liu, Z.; Shen, H.; Xiao, H.; Wang, Z.; Zhu, L.; Li, C. *Org. Lett.* **2019**, *21*, 5201−5205.
(19) He, T.; Gao, W. C.; Wang, W. K.; Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 1113−1118.

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