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Hydrogen-Bond-Guided Reaction of Cyclohexadienone-aldehydes with Amines: Synthesis of an Aminal Group Containing a Fused Tetracyclic Framework

Anil Chauhan, Raj Kumar Patel, Mary Grellier,* and Ravindra Kumar*

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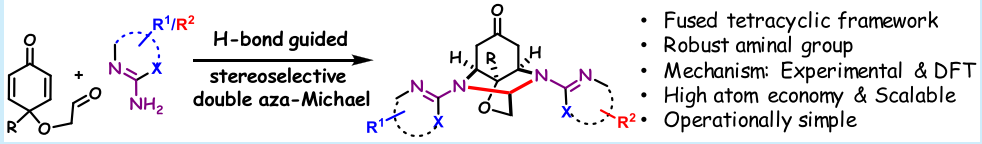
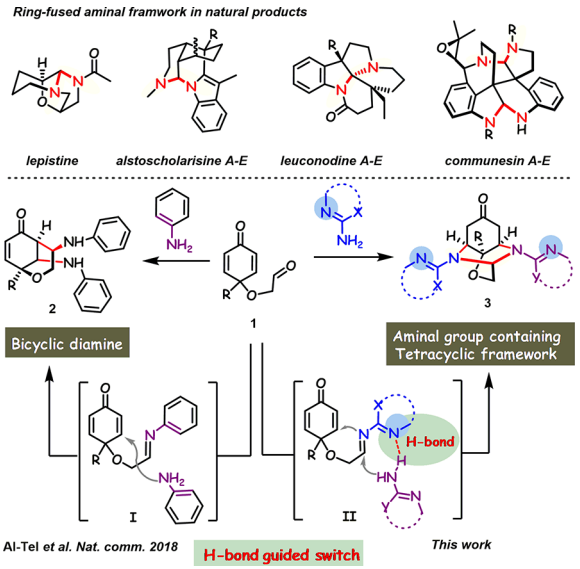


ABSTRACT: A modular approach has been developed for an efficient synthesis of an aminal group containing a new tetracyclic framework. The strategy has been devised based on selective hydrogen-bond-guided aza-Michael addition of heteroaromatic amines to cyclohexadienone-aldehydes. The reaction is highly atom economic and practical and involves stereoselective construction of four new C−N bonds and four rings. The synthetic utility of the tetracyclic product was explored. The role of a H-bond was explained with the help of experimental and density functional theory (DFT) computation studies.

The sp^3-rich molecular complexity of the natural products has always been an inspiration for the development of a newer strategy for target-oriented and diversity-oriented organic synthesis.[1] Although the ring-fused aminal (N−C−N) system is frequently found in naturally occurring alkaloids (Scheme 1),[2] the stereoselective and step-economical synthesis of this core is quite challenging due to its inherent chemical reactivity. A domino reaction often provides a modular approach to complex molecular architectures, which can be envisioned from the design of suitable starting materials having multiple reactive points.[3] Suitably substituted symmetrical cyclohexadienones, which are readily available through oxidation of phenols, are an ideal substrate in this regard.[4−7] A catalytic desymmetrization strategy has been widely explored with the suitably substituted (alkene/alkyne) symmetrical cyclohexadienones to afford bicyclic[5] and tricyclic[6] frameworks. Cyclohexadienone tethered with an aldehyde **1** could also be a multifunctional synthon to generate molecular complexity; however, it was remarkably less explored.[7] Al-Tel et al. have elegantly investigated the reactivity of symmetrical aldehyde **1** with various amines, in which aniline was reported to give a desymmetrized bicyclic diamine product **2** through usual aza-Michael reaction on dienone-imine (**I**, Scheme 1).[7b] Given the importance of H-bonding that often dictates the reactivity profile, nitrogen-containing heteroaromatic amines were sought to be explored. It was envisioned that nitrogen in an aromatic ring may impart H-bonding that may switch the reactivity of amine toward symmetrical cyclohexadienone-aldehyde **1** (**II**, Scheme 1). Herein, we report H-bond-guided selective synthesis of an aminal group containing symmetrical

Scheme 1. Ring-Fused Aminal (N−C−N) Group Containing Natural Products and Stereoselective Reaction of Cyclohexadienone-aldehyde with Aromatic Amines



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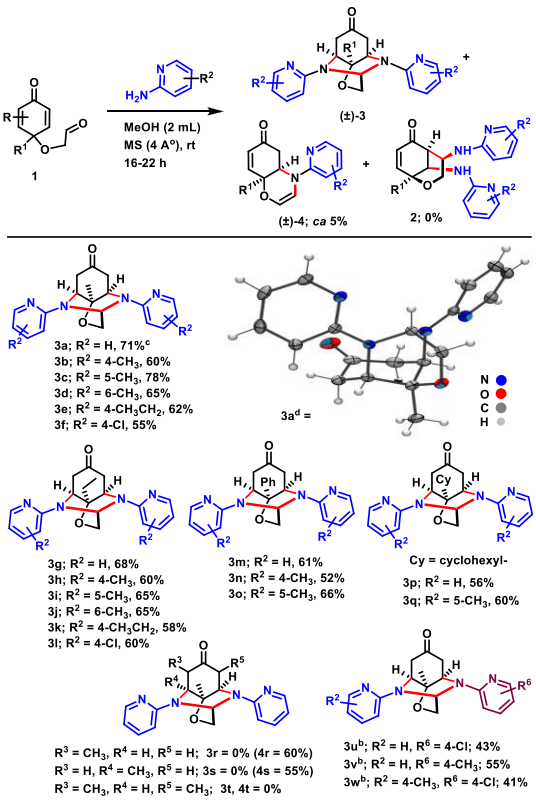
and unsymmetrical fused tetracyclic scaffolds **3** for the first time (Scheme 1).

The modular reaction of cyclohexadienone-aldehyde **1a** with 2-aminopyridine gave a mixture of **3a** and **4a** in 71% and 5% yields, respectively, as a single diastereomer for each in methanol at room temperature (Scheme 2). The corresponding bicyclic diamine product **2a** was never obtained, as reported previously with simple aniline.[7b] The structure of **3a** was unequivocally established by a single-crystal X-ray,[8] showing the formation of a new tetracyclic framework, having an aminal group (Scheme 2).

Scheme 2. Reaction of 1a with 2-Aminopyridine[a]

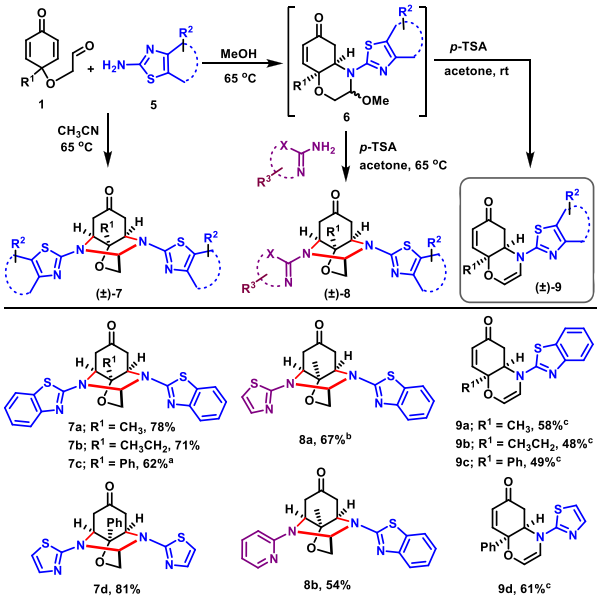


[a]Conditions: **1** (0.5 mmol), aminopyridine (2.2 equiv). Isolated yields are mentioned. [b]Aminopyridines (1.1 equiv each) were employed. [c]Gram-scale synthesis was conducted (1.6 g, 73% yield). [d]Ellipsoid structure of **3a** is shown with 50% probability level. See Table S1 for the optimization study.[8]

The substrate scope was investigated by varying cyclohexadienone-aldehydes **1** and 2-aminopyridines (Scheme 2). 4-Methyl-, 5-methyl-, 6-methyl-, 4-ethyl-, and 4-chloro-2-aminopyridine gave the corresponding tetracyclic products (**3b**–**f**; 55–78% yields) with **1a**. Variation in substituents at the fourth position of **1** gave the corresponding 4-ethyl- (**3g**–**l**; 58–68% yields), 4-phenyl- (**3m**–**o**; 52–66% yields), and 4-cyclohexyl- (**3p** and **3q**; 56% and 60% yields) substituted tetracyclic products. However, polysubstituted cyclohexadienone-aldehydes failed to give the desired tetracyclic products (**3r**–**t**), probably due to steric congestion. However, the corresponding bicyclic products (**4r** and **4s**; 60% and 55% yields, respectively) were obtained from 2,4-dimethyl- and 3,4-dimethyl-substituted aldehydes (Scheme 2). Unsymmetrical tetracyclic products could also be obtained by the reaction of **1a** with two different 2-aminopyridines (**3u**–**3w**; 41–55% yields, Scheme 2).

The reaction scope of cyclohexadienone-aldehyde **1** was further investigated with 2-aminothiazoles (Scheme 3). 2-Aminobenzothiazole (**5a**) gave a solely hemiaminal product **6a** in methanol at 65 °C (Scheme 3). Change of solvent to acetonitrile gave tetracyclic products (**7a**–**d**; 62–81% yields) with no formation of bicyclic byproducts **9** (like **4**) (Scheme 3). The inherent reactivity of the hemiaminal intermediate (**6**) was subsequently exploited with 2-aminothiazole and 2-aminopyridine in the presence of *p*-TSA, giving unsymmetrical tetracyclic products (**8a** and **8b** in 67% and 54% yields, respectively; Scheme 3), whereas bicyclic products (**9a**–**d**) were obtained at room temperature in the absence of any amine (Scheme 3).

Scheme 3. Reaction of 1 with 2-Aminothiazoles[a]



[a]Conditions: **1** (0.5 mmol), thiazole (2.2 equiv), solvent (2 mL). Isolated yields are mentioned. [b]Gram-scale synthesis was conducted (1.17 g, 71% yield). [c]Yields are over two steps.

The practical applicability of the present reaction was evaluated with gram-scale syntheses for **3a** (1.60 g, 73%; Scheme 2) and **8a** (1.17 g, 71%; Scheme 3).[8] Furthermore, the tetracyclic structures have interesting cage-like molecular architecture and latent functional handles, such as the carbonyl and aminal groups, encouraged us to explore their synthetic utility (Scheme 4). Reduction of carbonyl with $NaBH_4$ gave secondary alcohol **10** in 89% yield (dr = 7:1). Ketone **3a** was converted into ring-fused seven-membered lactam **12** in 55% yield through an oxime intermediate **11**,[9,10] whereas an oxime **11** was synthesized in 87% yield from **3a**.[11] The carbon functionality at the carbonyl carbon was introduced by palladium-catalyzed cross-coupling reactions between the corresponding enol-triflate (**13**) and various coupling partners (Ph, H, alkyne; **14**–**16**). The reactivity of the aminal group was investigated under acidic conditions. The selective cleavage of an aminal C–N bond gave a bicyclic diamine product (**17**, single diastereomer, 75%) in the presence of trifluoromethanesulfonic acid, whereas bicyclic product **4a** was obtained in 69% yield in the presence of acetic acid (Scheme 4).

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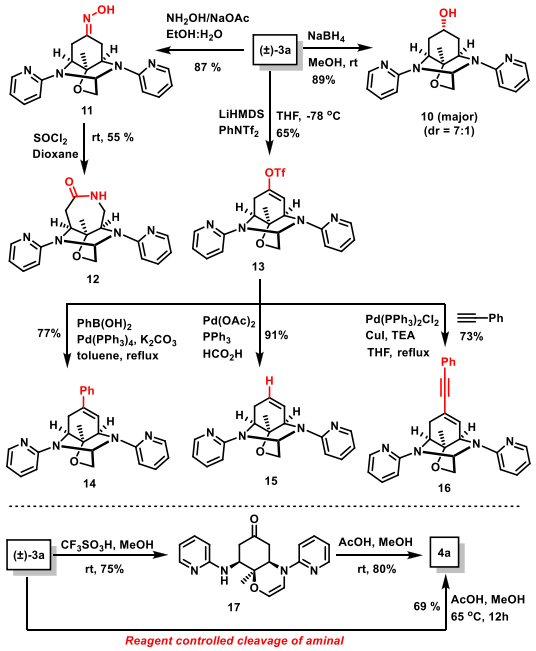
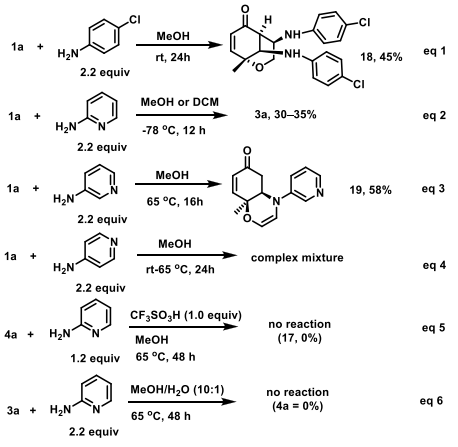
Scheme 4. Synthetic Transformations of 3a



[a]Isolated yields are mentioned.

In order to gain deeper insight into a possible reaction mechanism and the cause of product switch (**2** vs **3**), a series of controlled experiments were conducted (Scheme 5). The

Scheme 5. Control Experiments



reaction between **1a** and 4-chloroaniline in MeOH did not give the corresponding tetracyclic product **3**, and a solely bicyclic diamine product was obtained in 45% yield (**18**, like **2**; eq 1). The reaction of **1a** with 2-aminopyridine at −78 °C in methanol (as well as in DCM) gave **3a** (30−35% yield; eq 2). In both solvents, the corresponding bicyclic diamine product was not obtained. These experiments suggest that neither solvent nor temperature is the origin of the product switch. To check the key involvement of the H-bond from neighboring nitrogen, reactions were investigated with 3- and 4-amino-pyridines (eqs 3 and 4). There was no formation of corresponding tetracyclic products. It reveals that precisely positioned neighboring aromatic nitrogen might take part in H-bonding[12] with another 2-aminopyridine to bring it closer to being attacked on imine to form the aminal (N−C−N) bond.

On the other hand, when **4a** was heated exclusively with 2-aminopyridine in MeOH (or in the presence of CF_3SO_3H; eq 5), there was no reaction. It advocates that desymmetrization of enone through the usual aza-Michael reaction would be a less likely pathway for the synthesis of **3**. The minor product **4** was also confirmed to not be formed from **3** by thermal decomposition (eq 6, Scheme 5).

To further support our hypothesis, density functional theory (DFT) calculation was conducted, considering the imine and the 2-aminopyridine as the reference system (**A0**).[8] Both reaction pathways leading to tetracyclic product **3a** and the bicyclic product **4a** are exergonic (ΔG = −26.4 and −13.9 kcal mol^{-1}, respectively; Figure 1). We have selected the condensed

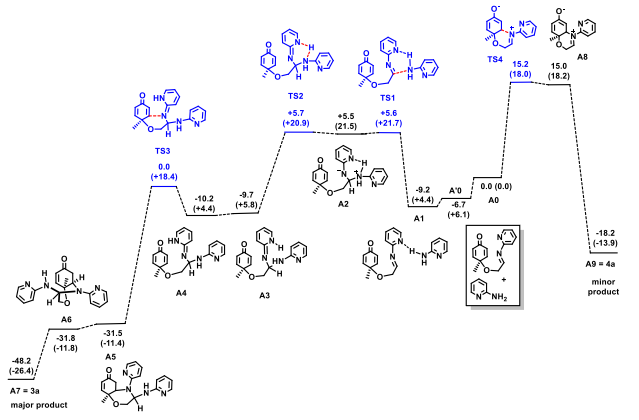


Figure 1. DFT calculation E in kcal mol^{-1}; In parentheses (), ΔG in kcal mol^{-1}. In blue: transition states (TS). In red dotted line: bonds formed and/or broken at the TS. The **TS4**, **A8**, and **A9** energy values presented take into account the contribution of one additional free 2-aminopyridine energy.

local nucleophilicity index (N_k) to compare the nucleophilicity of nitrogen. The "N" index was associated with the condensed local Fukui function (f_k^-) by the following relation $N_k = N^* f_k^-$. The N_k values obtained with different aminopyridines are shown in Table 1. A higher value of the N_k index is

Table 1. Nucleophilicity Indexes[a]

entry	compound	N	f_k^-	N_k
1	2-aminopyridine	2.86	0.269	0.77
2	3-aminopyridine	3.08	0.278	0.86
3	4-chloroaniline	4.13	0.240	0.99
4	**AO**	2.21	0.137	0.30
5	**A1**	3.16	0.288	0.91
6	**A3**	3.36	0.299	1.01

[a]The values rely on the nitrogen involved in the nucleophilic attack to the enone/imine fragment (see SI for the calculation details).

equivalent to better nucleophilicity of the corresponding nitrogen. Considering the N_k values, 4-chloroaniline is a better nucleophile than 2-aminopyridine and 3-aminopyridine (entries 1−3, Table 1). This first comparison is in agreement with the synthesis of the bicyclic diamine product **18** (like **2**), as the first step could be the nucleophilic attack at the C_β position in cyclohexadienone (eq 1, Scheme 5). The possibility to form the ring is unfavorable due to the low nucleophilicity of the imine nitrogen (**A0**, entry 4, Table 1 and Figure 1). The possible formation of a H-bond between imine and 2-aminopyridine, inside the solvation cavity, is slightly ender-

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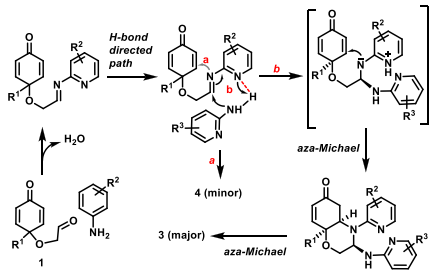
gonic (see Figure 1). This formation enhances the nucleophilicity of the 2-aminopyridine fragment (N_k values: 0.77 to 0.91; entries 1 and 5, respectively). H-bonded preorganization of **A1** followed by hydrogen transfer to the pyridine-N led to a new intermediate **A3** (see Figure 1). The activation associated with the formation of **A3** is the rate-determining step for ring closure. The nucleophilicity of the nitrogen center involved in the ring closure (**A3**) increases dramatically (N_k = 1.01, entry 6), which is in the same order of magnitude as in 4-chloroaniline (entry 3). The ring closure could occur in a concerted process involving the formation of the N−C bond and hydrogen transfer (see video in the Supporting Information). Conformation changes of the six aza-membered rings from **A5** to **A6** and subsequent attack of nitrogen to the electrophilic C_β position on cyclohexenone led to tetracyclic product **3a** (= **A7**). Alternatively, the synthesis of minor product **4a** (= **A9**) has also been investigated by calculations (see molecular orbital frontiers in the Supporting Information).[8] Thus, a plausible reaction mechanism has been proposed based on a previous report[12] and experimental and DFT studies. H-bond-directed addition of 2-aminopyridine to an imine followed by aza-Michael to cyclohexadienone gives an aminal intermediate, which on subsequent aza-Michael reaction leads to a tetracyclic product (Path A, Scheme 6).

Scheme 6. Plausible Mechanism



In conclusion, a H-bond-guided stereoselective double aza-Michael strategy has been developed for an efficient synthesis of aminal-group-containing tetracyclic fused scaffolds. The developed method is the mildest so far reported for such a complex tetracyclic framework. The reaction is highly atom economic and operationally simple. Controlled experimental and DFT calculation studies were conducted to draw the plausible reaction mechanism. Detailed studies of the reaction mechanism and further exploration of desymmetrization strategy on cyclohexadienone-aldehyde are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02284.

Experimental procedures, spectroscopic analytical data for all new compounds, and DFT computation data (PDF)

Video connecting A4 and A5 via TS3 (MOV)

Accession Codes

CCDC 2001483 contains 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.

■ AUTHOR INFORMATION

Corresponding Authors

Ravindra Kumar − *Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow 226031, UP, India; Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India;* orcid.org/0000-0003-0290-679X; Email: ravindra.kumar1@cdri.res.in

Mary Grellier − *LCC-CNRS, Université de Toulouse, CNRS, UPS, Toulouse F-31077 Cedex 4, France;* Email: mary.grellier@lcc-toulouse.fr

Authors

Anil Chauhan − *Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow 226031, UP, India; Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India*

Raj Kumar Patel − *Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow 226031, UP, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02284

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 48−56.

(2) For representative examples: (a) Wood, M. D.; Klosowski, D. W.; Martin, S. F. *Org. Lett.* **2020**, *22*, 786−790. (b) Park, J.; Jean, A.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2017**, *56*, 14237−14240. (c) Pfaffenbach, M.; Gaich, T. *Chem. - Eur. J.* **2016**, *22*, 3600−3610. (d) Yang, Y.; Bai, Y.; Sun, S.; Dai, M. *Org. Lett.* **2014**, *16*, 6216−6219. (e) Kitabayashi, Y.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2014**, *16*, 2862−2864.

(3) (a) *Domino Reactions: Concepts for Efficient Organic Synthesis*; Tietze, L. F., Ed.; Wiley-VCH: Weinheim, 2014. (b) Green, N. J.; Sherburn, M. S. *Aust. J. Chem.* **2013**, *66*, 267−283.

(4) (a) Kalstabakken, K. A.; Harned, A. M. *Tetrahedron* **2014**, *70*, 9571−9585. (b) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068−4093. (c) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383−1430.

(5) (a) Zhang, J.-L.; Gao, D.; Tan, Y.-X.; He, C.-Y.; Peng, P.-Y.; Lin, G.-Q.; Li, Q.-H.; Tian, P. *Org. Lett.* **2020**, *22*, 3661−3666. (b) Tan, Y.-X.; Zhang, F.; Xie, P.-P.; Zhang, S.-Q.; Wang, Y.-F.; Li, Q.-H.; Tian,

P.; Hong, X.; Lin, G.-Q. *J. Am. Chem. Soc.* **2019**, *141*, 12770−12779. (c) Nair, A. M.; Kumar, S.; Volla, C. M. R. *Adv. Synth. Catal.* **2019**, *361*, 4983−4988. (d) Ma, X.-L.; Wang, Q.; Feng, X.-Y.; Mo, Z.-Y.; Pan, Y.-M.; Chen, Y.-Y.; Xin, M.; Xu, Y.-L. *Green Chem.* **2019**, *21*, 3547−3551. (e) Han, S.; Liu, S.; Liu, L.; Ackermann, L.; Li, J. *Org. Lett.* **2019**, *21*, 5387−5391. (f) Tan, Y.-X.; Liu, X.-Y.; Zhao, Y.-S.; Tian, P.; Lin, G.-Q. *Org. Lett.* **2019**, *21*, 5−9. (g) Kumaraswamy, G.; Gangadhar, M.; Ramesh, V.; Ankamma, K.; Sridhar, B. *Org. Lett.* **2019**, *21*, 6300−6304. (h) Mallick, R. K.; Dutta, S.; Vanjari, R.; Voituriez, A.; Sahoo, A. K. *J. Org. Chem.* **2019**, *84*, 10509−10517. (i) Tan, Y.-X.; Tang, X.−Q.; Liu, P.; Kong, D.-S.; Chen, Y.-L.; Tian, P.; Lin, G.-Q. *Org. Lett.* **2018**, *20*, 248−251. (j) Li, K.; Jin, Z.; Chan, W.-L.; Lu, Y. *ACS Catal.* **2018**, *8*, 8810−8815. (k) Yao, W.; Dou, X.; Wen, S.; Wu, J.; Vittal, J. J.; Lu, Y. *Nat. Commun.* **2016**, *7*, 13024. (l) Clarke, C.; Incerti-Pradillos, C. A.; Lam, H. W. *J. Am. Chem. Soc.* **2016**, *138*, 8068−8071. (m) Murthy, A. S.; Donikela, S.; Reddy, C. S.; Chegondi, R. *J. Org. Chem.* **2015**, *80*, 5566−5571. (n) Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 11700−11703.

(6) (a) Thopate, S. B.; Jadhav, S. B.; Nanubolu, J. B.; Chegondi, R. *ACS Catal.* **2019**, *9*, 10012−10019. (b) Shu, T.; Zhao, L.; Li, S.; Chen, X.-Y.; Essen, C. v.; Rissanen, K.; Enders, D. *Angew. Chem., Int. Ed.* **2018**, *57*, 10985−10988. (c) Kumar, R.; Hoshimoto, Y.; Tamai, E.; Ohashi, M.; Ogoshi, S. *Nat. Commun.* **2017**, *8*, 32. (d) Xu, G.; Liu, K.; Sun, J. *Org. Lett.* **2017**, *19*, 6440−6443. (e) Zhao, F.; Li, N.; Zhu, Y.-F.; Han, Z.-Y. *Org. Lett.* **2016**, *18*, 1506−1509.

(7) (a) Srinivasulu, V.; Khanfar, M.; Omar, H. A.; ElAwady, R.; Sieburth, S. M.; Sebastian, A.; Zaher, D. M.; Al-Marzooq, F.; Hersi, F.; Al-Tel, T. H. *J. Org. Chem.* **2019**, *84*, 14476−14486. (b) Srinivasulu, V.; Schilf, P.; Ibrahim, S.; Khanfar, M. A.; Sieburth, S. M.; Omar, H.; Sebastian, A.; AlQawasmeh, R. A.; O'Connor, M. J.; Al-Tel, T. H. *Nat. Commun.* **2018**, *9*, 4989. (c) Martin-Santos, C.; Jarava-Barrera, C.; del Pozo, S.; Parra, A.; Diaz-Tendero, S.; Mas-Balleste, R.; Cabrera, S.; Aleman, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 8184−8189. (d) Vo, N. T.; Pace, R. D. M.; O'Har, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404−405. (e) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552−2553.

(8) See Supporting Information for details.

(9) Direct use of NaN_3 and $TMSN_3$ failed to give **12**. Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Praneeth, K. *Tetrahedron Lett.* **2008**, *49*, 4742−4745.

(10) Liu, Z.-J.; Lu, X.; Wang, G.; Li, L.; Jiang, W.-T.; Wang, Y.-D.; Xiao, B.; Fu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 9714−9719.

(11) Mo, X.; Morgan, T. D. R.; Ang, H. T.; Hall, D. G. *J. Am. Chem. Soc.* **2018**, *140*, 5264−5271.

(12) Al-Warhi, T. I.; Al-Hazimi, H. M. A.; El-Faham, A. *J. Saudi Chem. Soc.* **2012**, *16*, 97−116.

https://dx.doi.org/10.1021/acs.orglett.0c02284
Org. Lett. XXXX, XXX, XXX−XXX