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Me₂(CH₂=CH)SiCN: a bifunctional ethylene equivalent for Diels–Alder reaction based controllable tandem synthesis†

Wen-Biao Wu,^a Bo-Shuai Mu,^a Jin-Sheng Yu[✉]*^{ab} and Jian Zhou[✉]^{abc}

A bifunctional silyl reagent Me₂(CH₂=CH)SiCN has been developed as a novel ethylene equivalent for the Diels–Alder (DA) reaction. The use of this reagent enables the controllable synthesis of value-added cyclohexenyl ketones or 2-acyl cyclohexancarbonitrile derivatives through a five- or six-step tandem sequence based on a Wittig/cyano-silylation/DA reaction/*retro*-cyano-silylation/isomerization sequence that involves a temporary silicon-tethered intramolecular DA reaction.

Introduction

The Diels–Alder (DA) reaction is one of the most important C–C bond-forming reactions for building up molecular complexity.¹ Since its discovery, many types of functionalized dienes and dienophiles have been designed and applied for the synthesis of structurally diverse cyclohexenes with control of facial, regio- and stereoselectivity.² Usually, DA reactions proceed smoothly when the dienophiles are activated by electron-withdrawing groups. When it comes to cycloaddition of ethylene, which is a commonly required synthetic step, the conditions entail very high temperature and pressure,³ which are often too harsh to be used easily (Scheme 1a). Therefore, the development of ethylene equivalents that can be used for DA reactions under milder conditions has received great attention. To date, vinyl sulfide⁴ or sulfone,⁵ nitroethylene,⁶ vinylidihaloboranes,⁷ acrolein,⁸ and selenoacrylate⁹ have been utilized as ethylene surrogates for DA reactions (Scheme 1b). The electron-withdrawing groups of the corresponding adducts can be removed subsequently through a single or multi-step transformation.⁸ Despite these advances, it is still important to develop new ethylene surrogates to facilitate the cycloaddition and subsequent removal of activating groups, and, in particular, to allow structural reorganization following the DA reaction, which can enable access to cyclohexene derivatives that are inaccessible by the direct [4+2] process.

On the other hand, the use of a temporary silicon tether to connect two reaction partners and induce an intramolecular reaction has been established as a powerful strategy to enhance both the reactivity and selectivity, owing to the innate benefits of intramolecularity.¹⁰ Since the independent pioneering studies of Nishiyama¹¹ and Stork,¹² this strategy has found numerous applications in organic synthesis,¹⁰ including diverse synthesis of cyclohexenes through DA cycloaddition of silicon-tethered dienes and dienophiles.¹³ These elegant advances encouraged us to develop silicon-tethered ethylene equivalents for DA reactions. It is worth mentioning that traditional methods to introduce silicon tethers and labile Si–O bonds rely on the protection of the O–H bond using the corresponding chlorosilyl reagents. Instead, we aim to develop bifunctional

^aShanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, Shanghai Key Laboratory of Green Chemistry and Chemical Processes, East China Normal University, Shanghai 200062, China. E-mail: jsyu@chem.ecnu.edu.cn

^bKey Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, Hainan Normal University, Haikou 571158, China

^cInstitute of Eco-Chongming, Shanghai 202162, China

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Scheme 1 State-of-the-art and present work.

Scheme 2 Synthesis of **1** and its application in the tandem sequence of cyanosilylation and the DA reaction.

silyl reagents (BSR) that can add to $\text{C}=\text{O}$ double bonds to generate the Si–O bond tethering two functionalities for further transformations. This strategy proved to be workable because our reagent, $\text{Me}_2(\text{CH}_2\text{Cl})\text{SiCN}$,¹⁴ enabled facile access to α -chloroacetyl tertiary alcohols through a tandem asymmetric cyanosilylation-chloromethyl transferring sequence.

Accordingly, a new BSR reagent, $\text{Me}_2(\text{CH}_2=\text{CH})\text{SiCN}$ (**1**), was designed as an ethylene equivalent for the following reasons. First, it can enable the use of acyclic α,β,γ , and δ -unsaturated aldehydes or ketones **2** that have not been used as dienes to react with ethylene or known surrogates (Scheme 1c). The initial cyanosilylation¹⁵ affords cyanohydrins **3** featuring a Si–O bond tethered diene and a vinyl moiety for the DA reaction. A further *retro*-cyanosilylation,¹⁶ with simultaneous cleavage of the C–Si bond under mild conditions, readily releases the ketone moiety from adduct **4** to fulfill formal cycloaddition using dienones **2**. Second, it allows tandem synthesis of cyclohexene derivatives

that are unattainable by using the normal $[4+2]$ route. Once *retro*-cyanosilylation occurs, it is possible to control the reaction conditions to achieve the selective synthesis of enones **5** resulting from the conjugation of the ketone moiety with the alkene, or cyclohexenes **6** substituted by the cyano and acetyl group. Both cyclohexene derivatives **5** and **6** are useful synthons¹⁷ with two functionalities. Herein, we wish to report that the development of ethylene equivalent **1** enables a controllable synthesis of valuable cyclohexene derivatives with structural diversity through a tandem cyanosilylation/DA reaction/*retro*-cyanosilylation sequence, by taking advantage of a temporary silicon-tethered DA reaction (Scheme 1c).

Results and discussion

Optimization of the reaction conditions

We began this study by exploring the synthesis of BSR **1**. To our delight, we found that it could be readily obtained in 80% yield from NaCN and $\text{Me}_2(\text{CH}_2=\text{CH})\text{SiCl}$ on a 740 mmol scale using the procedure for preparing $\text{Me}_2(\text{CH}_2\text{Cl})\text{SiCN}$ ^{14a} (Scheme 2a). Furthermore, the cyanosilylation of α,β,γ , and δ -unsaturated enone **2a** using **1** was found to work well in the presence of 10 mol% acetone-derived P-ylide **7a**,^{18a} giving the desired silyl cyanohydrin **3a** in 85% yield (Scheme 2b). With the silicon-tethered triene **3a**, bearing both a diene and a vinyl group at hand, we next investigated its intramolecular DA reaction, and found that it proceeded well under thermal conditions. Full conversion of **3a** was observed in toluene at 120 °C by GC-MS and ¹H NMR analysis of the crude reaction mixture, giving the desired DA adduct **4a** as a mixture of diastereomer (for details, see Section 3.2 of the ESI†). This finding paved the way for the desired merging of a *retro*-cyanosilylation step for tandem synthesis of cyclohexene derivatives. The evaluation of typical desilylation conditions to convert adduct **4a** into cyclohexenyl methyl ketone **5a** revealed that the use of a stoichiometric amount of TBAF was the best choice, but the fluoride that was formed *in situ* might lead to side Michael addition to give 2-acetyl-5-phenylcyclohexanecarbonitrile **6a**.¹⁹ Further studies focused on the controllable synthesis of **5a** and **6a** given that both are useful synthons.¹⁷ For the selective synthesis of **5a**, we tried adding metal salts to mask the cyanide,²⁰ and $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ proved to be optimal (for details, see the ESI†).

Scheme 3 Switchable divergent tandem synthesis of cyclohexenyl methyl ketone **5a** and 2-acetyl-5-phenylcyclohexanecarbonitrile **6a**. The overall isolated yield was reported. The dr values were determined by ¹H NMR analysis of the crude reaction mixture.

Accordingly, the synthesis of **5a** was achieved in 73% yield in toluene by using TBAF and $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (Scheme 2c). On the other hand, the use of EtOAc as the solvent, along with TBAF (70 wt% in H_2O) led to the generation of **6a** with 64% yield and >20 : 1 dr as the major product.

Having established the optimal conditions for the controllable synthesis of cyclohexene derivatives **5a** and **6a** via DA reaction/*retro*-cyanosilylation based transformations, we tried combining the Wittig synthesis of α,β,γ , and δ -unsaturated enone **2a** and cyanosilylation to form a five- or six-step tandem sequence starting from P-ylide **7a**, enal **8a**, and **1**. Notably, although very few tandem reactions consisting of five steps and more are known,²¹ our sequences could work very efficiently (Scheme 3).

The initial Wittig reaction of P-ylide **7a** and enal **8a** proceeded smoothly at 80 °C in MeCN; a solvent required for the next cyanosilylation mediated by the excess P-ylide.^{18a} Once the cyanosilylation completed, the crude silyl cyanohydrins were collected and subjected to the DA reaction/*retro*-cyanosilylation sequence in either toluene or EtOAc. After heating at 120 °C for 16 h to allow the intramolecular DA reaction to complete, TBAF (1.0 M in THF) and $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ or TBAF (70 wt% in H_2O) was added at room temperature to facilitate the following *retro*-

cyanosilylation/isomerization or *retro*-cyanosilylation/isomerization/Michael addition, giving **5a** in 65% overall yield in five steps or **6a** in 55% overall yield in six steps with >20 : 1 dr, respectively (Scheme 3).

Evaluation of substrate scope

Next, we examined the generality of the synthesis of cyclohexenyl ketones **5** (Scheme 4). A variety of 3-aryl and 3-alkyl α,β -unsaturated aldehydes were compatible with the tandem Wittig/cyanosilylation/DA/*retro*-cyanosilylation/isomerization sequence, and worked well with ylide **7a** and $\text{Me}_2(\text{CH}_2=\text{CH})\text{SiCN}$ **1** to afford the corresponding cyclohexenyl methyl ketones **5a–o** in moderate to high yields. The use of β -(2-furyl) substituted enal delivered the product **5k** in 77% yield, and β -alkyl enals gave the desired products **5l–o** with slightly lower yields. Ethyl-, isopropyl-, cyclopropyl-, and phenyl-substituted P-ylides **7b–e** all worked well to afford the corresponding cyclohexenyl ketones **5p–s** in 50–75% yields. However, the low reactivity of isopropyl, cyclopropyl or phenyl substituted ylides required the addition of 1.0 mol% $\text{Ph}_3\text{P}=\text{CHCONEt}_2$ (**7f**)^{18a} as the catalyst for the cyanosilylation step. Additionally, 5-methyl-2-phenyl-2-hexenal was also workable, giving multi-substituted

Scheme 4 Scope of the tandem synthesis of substituted cyclohexenyl ketones **5**. Reaction conditions: **1** (2.0 mmol), **7** (1.1 mmol), **8** (1.0 mmol), TBAF (4.0 mL, 1.0 M in THF) and $\text{Mn}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.0 mmol). The dr values were determined by ¹H NMR analysis of the crude reaction mixture. ^a $\text{Ph}_3\text{P}=\text{CHCONEt}_2$ **7f** (1.0 mol%) was added in the cyanosilylation step. ^b**5s** was obtained from 1,5-diphenylpenta-2,4-dien-1-one via a cyanosilylation/Diels–Alder/*retro*-cyanosilylation/isomerization tandem reaction. ^cRun on a 0.5 mmol scale. ^dRun on a 0.3 mmol scale.

Scheme 5 Scope of the tandem synthesis of 2-acyl cyclohexanecarbonitriles **6**. Reaction conditions: **1** (2.0 mmol), **7** (1.1 mmol), **8** (1.0 mmol), and TBAF (4.0 mmol, 70 wt% in H₂O). The dr values were determined by ¹H NMR analysis of the crude reaction mixture. ^aPh₃P=CHCONEt₂ **7f** (1.0 mol%) was added as catalyst in the cyano-silylation reaction. ^b**6m** was obtained from (2*E*,4*E*)-6,6,6-trifluoro-1-phenylhexa-2,4-dien-1-one via a cyano-silylation/Diels–Alder/*retro*-cyano-silylation/isomerization/Michael addition sequence. ^cRun on a 0.5 mmol scale.

cyclohexenyl ketone **5t** in 32% yield with 1.5 : 1 dr. Notably, a range of five- and six-membered cyclic enals were also viable substrates, delivering valuable polycyclic compounds **5u–5aa**, featuring a cyclohexenyl ketone moiety in moderate to good yields with good to high dr values.

Moreover, this method was successfully applied to late-stage modification of estrone through the introduction of a cyclohexenyl ketone moiety, affording the pentacyclic product **5ab** in 69% yield and 12 : 1 dr. The structure and relative configuration were confirmed by X-ray analysis of products **5u**, **5x**, and **5ab**.

As shown in Scheme 5, the scope of the six-step tandem synthesis of 2-acyl cyclohexanecarbonitriles **6** was also evaluated under the optimized conditions. A series of 3-aryl substituted α,β -unsaturated aldehydes **8** were viable substrates, furnishing the desired products **6a–g** in 51–77% yield with 2.5 : 1 to >20 : 1 dr. 2-Furyl substituted enal provided the corresponding product **6h** in 83% yield with modest dr. Phenyl substituted phosphorus ylide **7e** also reacted smoothly with aryl- or alkyl-substituted enals to give 2-benzoylcyclohexane-1-carbonitrile derivatives **6i–l** in good yields and dr values. Interestingly, this protocol could be extended to access trifluoromethylated cyclohexane derivatives when CF₃-substituted enal was used, as shown by the formation of **6m** in 90% yield with 5.0 : 1 dr. The scope of

the reaction with substituted ylides was also examined, and it was found that isopropyl and cyclopropyl phosphoranes worked well to give the desired products **6n** and **6o** in 58% and 73% yield with 6.4 : 1 and 4.8 : 1 dr, respectively. To our delight, tricyclic compounds **6p–r**, with a 2-acetyl cyclohexanecarbonitrile moiety, could be readily generated through this sequence from the corresponding cyclic enals. X-ray analysis of both **6i** and **6r** confirmed their structure and the *cis* relative configuration of the cyano and carbonyl group; those of other products **6** were tentatively assigned.

Scheme 6 Synthetic transformations.

Scheme 7 Attempt to access chiral cyclohexenyl ketone 5a.

Synthetic utility

It should be noted that the cyclohexenyl ketone moiety is found widely in natural products and bioactive molecules. Although four major synthetic strategies have been developed to access this group,²² most are based on the conversion of cyclohexanone derivatives, which limits the structural diversity of the products. By contrast, our approach provides a facile and flexible route for the synthesis of structurally diverse cyclohexenyl ketones and their derivatives from simple reagents and α,β -unsaturated enals with either an acyclic or cyclic backbone. The synthetic utility of the cyclohexenyl ketones thus obtained was further highlighted by the application of various diversifying reactions (Scheme 6). For instance, *trans*-1-(4-phenylcyclohexyl)-1-ethanone **9** could be obtained in 68% yield with 7 : 1 dr *via* the selective hydrogenation of cyclohexenyl methyl ketone **5a** and sequential base-mediated epimerization (Scheme 6). Under the action of NaOH, **5a** worked with thiosemicarbazide or PhCHO to furnish thiosemicarbazone **10** and divinyl ketone **11** *via* imine formation or aldol condensation, respectively. Upon treatment with TIPSOTf and Et₃N, **5a** was converted into the corresponding silyl enol ether, which further underwent a DA reaction with ethyl propiolate to furnish bicyclic tetrahydronaphthalene derivative **12** in 40% yield after oxidation.

Finally, we attempted the synthesis of chiral cyclohexenyl ketone **5a** by integrating an asymmetric cyanosilylation into the sequence. However, while enantioenriched **3a** could be obtained in 88% yield with 90% ee by using the three-component catalyst system of (*R,R*)-salen(AlCl) **15**/ylide/Ph₃PO that we previously developed,^{18c} the relay of the chiral information of **3a** to the desired cyclohexenyl ketone was not efficient under the standard conditions, as evidenced by the access of **5a** with 42% ee and 76% yield (Scheme 7). Nevertheless, the result establishes the feasibility of using such a tandem sequence to access chiral cyclohexenyl ketone derivatives, and further work in this direction is now in progress in our lab.

Conclusions

We have developed a novel bifunctional silyl reagent, Me₂(CH₂=CH)SiCN, as an ethylene equivalent capable of undergoing a temporary silicon-tethered intramolecular DA

reaction through the addition to the C=O double bond of enones. The value of this reagent is demonstrated by an unprecedented five- or six-step tandem synthesis involving Wittig/cyanosilylation/DA reaction/*retro*-cyanosilylation, paving the way for controllable and diverse synthesis of cyclohexenyl ketones and 2-acyl cyclohexanecarbonitrile derivatives. The development of an asymmetric variant of this tandem synthesis and further application of this reagent are ongoing in our lab.

Data availability

All of the experimental data have been included in the ESI.† Crystallographic data can be obtained from the CCDC (1921832, 1917989, 2076484, 2083519, 2101568 and 2089395).

Author contributions

W.-B. Wu and B.-S. Mu performed the experiments; W.-B. Wu collected and analyzed the data. J.-S. Yu and J. Zhou directed the project and co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98–122; (b) E. J. Corey, *Angew. Chem., Int. Ed.*, 2002, **41**, 1650–1667; (c) K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668–1698; (d) K. Takao, R. Munakata and K. Tadano, *Chem. Rev.*, 2005, **105**, 4779–4807; (e) M. Juhl and D. Tanner, *Chem. Soc. Rev.*, 2009, **38**, 2983–2992.
- (a) D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187–238; (b) F. Fringuelli and A. Taticchi, *The Diels–Alder Reaction—Selected Practical Methods*, Wiley, Chichester, 2002.
- (a) L. M. Joshel and L. W. Butz, *J. Am. Chem. Soc.*, 1941, **63**, 3350–3351; (b) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, 1964, **29**, 160–163; (c) D. Bartlett and K. E. Schueller, *J. Am. Chem. Soc.*, 1968, **90**, 6071–6077; (d) R. Golden and L. M. Stock, *J. Am. Chem. Soc.*, 1972, **94**, 3080–3088; (e) H. Takeshita, T. Hatsui, I. Shimooda and H. Mametsuka, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 2291–2292; (f) H. Takeshita, H. Kawakami, Y. Ikeda and A. Mori, *J. Org.*

- Chem.*, 1994, **59**, 6490–6492; (g) J. J. McNally and J. B. Press, *J. Org. Chem.*, 1991, **56**, 245–251.
- 4 K. Wiesner, T. Y. R. Tsai, G. I. Dmitruenko and K. P. Nambiar, *Can. J. Chem.*, 1976, **54**, 3307–3309.
- 5 (a) R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.*, 1980, **102**, 853–855; (b) C. V. R. Carr, R. V. Williams and L. A. Paquette, *J. Org. Chem.*, 1983, **48**, 4976–4986; (c) W. A. Kinney, G. D. Crouse and L. A. Paquette, *J. Org. Chem.*, 1983, **48**, 4986–5000. For the application in total synthesis, see: (d) J. R. Bull and K. Bischofberger, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2859–2865; (e) T. Omodani and K. Shishido, *J. Chem. Soc., Chem. Commun.*, 1994, 2781–2782; (f) S. Dalai, V. N. Belov, S. Nizamov, K. Rauch, D. Finsinger and A. de Meijere, *Eur. J. Org. Chem.*, 2006, 2753–2765.
- 6 N. Ono, H. Miyake, A. Kamimura and A. Kaji, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1929–1935.
- 7 M. Zaidlewicz, J. R. Binkul and W. Sokol, *J. Organomet. Chem.*, 1999, **580**, 354–362.
- 8 E. Taarning and R. Madsen, *Chem.–Eur. J.*, 2008, **14**, 5638–5644.
- 9 M. E. Jung, F. Perez, C. F. Regan, S. W. Yi and Q. Perron, *Angew. Chem., Int. Ed.*, 2013, **52**, 2060–2062.
- 10 For reviews, see: (a) M. Bols, *Chem. Rev.*, 1995, **95**, 1253–1277; (b) S. Bracegirdle and E. A. Anderson, *Chem. Soc. Rev.*, 2010, **39**, 4114–4129.
- 11 H. Nishiyama, T. Kitajima, M. Matsumoto and K. Itoh, *J. Org. Chem.*, 1984, **49**, 2298–2300.
- 12 G. Stork and M. Kahn, *J. Am. Chem. Soc.*, 1985, **107**, 500–501.
- 13 (a) K. Tamao, K. Kobayashi and Y. Ito, *J. Am. Chem. Soc.*, 1989, **111**, 6478–6480; (b) K. J. Shea, K. S. Zandi, A. J. Staab and R. Carr, *Tetrahedron Lett.*, 1990, **31**, 5885–5888; (c) D. Craig and J. C. Reader, *Tetrahedron Lett.*, 1990, **31**, 6585–6588; (d) J. W. Gillard, R. Fortin, E. L. Grimm, M. Maillard, M. Tjepkema, M. A. Bernstein and R. Glaser, *Tetrahedron Lett.*, 1991, **32**, 1145–1148; (e) K. J. Shea, A. J. Staab and K. S. Zandi, *Tetrahedron Lett.*, 1991, **32**, 2715–2718; (f) D. Craig and J. C. Reader, *Tetrahedron Lett.*, 1992, **33**, 4073–4076; (g) S. N. Sieburth and L. Fensterbank, *J. Org. Chem.*, 1992, **57**, 5279–5281; (h) G. Stork, T. Y. Chan and G. A. Breault, *J. Am. Chem. Soc.*, 1992, **114**, 7578–7579; (i) P. J. Coelho and L. Blanco, *Synlett*, 2001, **9**, 1455–1457.
- 14 Selected examples in developing bifunctional silyl reagents: (a) X.-P. Zeng and J. Zhou, *J. Am. Chem. Soc.*, 2016, **138**, 8730–8733; (b) X. Ye, X.-P. Zeng and J. Zhou, *Huaxue Xuebao*, 2016, **74**, 984–989; (c) C. Chen, W.-B. Wu, Y.-H. Li, Q.-H. Zhao, J.-S. Yu and J. Zhou, *Org. Lett.*, 2020, **22**, 2099–2104; (d) W.-B. Wu, X. Yu, J.-S. Yu, X. Wang, W.-G. Wang and J. Zhou, *CCS Chem.*, 2021, **3**, 2168–2180; (e) P.-W. Xu, X.-Y. Cui, C. Chen, F. Zhou, J.-S. Yu, Y.-F. Ao and J. Zhou, *Org. Lett.*, 2021, **23**, 8471–8476.
- 15 For selected recent reviews: (a) F.-X. Chen and X. Feng, *Curr. Org. Synth.*, 2006, **3**, 77–97; (b) J.-M. Brunel and I. P. Holmes, *Angew. Chem., Int. Ed.*, 2004, **43**, 2752–2778; (c) W. Wang, X. Liu, L. Lin and X. Feng, *Eur. J. Org. Chem.*, 2010, **2010**, 4751–4769; (d) H. Pellissier, *Adv. Synth. Catal.*, 2015, **357**, 857–882; (e) N. Kurono and T. Ohkuma, *ACS Catal.*, 2016, **6**, 989–1023; (f) X.-P. Zeng, J.-C. Sun, C. Liu, C.-B. Ji and Y.-Y. Peng, *Adv. Synth. Catal.*, 2019, **361**, 3281–3305; (g) W.-B. Wu, J.-S. Yu and J. Zhou, *ACS Catal.*, 2020, **10**, 7668–7690.
- 16 (a) H. Kunz and H. Waldmann, Protecting Groups, in *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991; (b) D. A. Evans, J. M. Hoffman and L. K. Truesdale, *J. Am. Chem. Soc.*, 1973, **95**, 5822–5823; (c) G. Stork and G. Kraus, *J. Am. Chem. Soc.*, 1976, **98**, 6747–6748; (d) T. Ohnuma, N. Hata, H. Fujiwara and Y. Ban, *J. Org. Chem.*, 1982, **47**, 4713–4717; (e) D. E. Ward and M. M. Zahedi, *Org. Lett.*, 2012, **14**, 6246–6249.
- 17 Cyclohexenyl methyl ketones are privileged structures in natural products, see: (a) Y.-Y. Lai, M.-C. Lu, L.-H. Wang, J.-J. Chen, L.-S. Fang, Y.-C. Wu and P.-J. Sung, *Mar. Drugs*, 2015, **13**, 4296–4309; (b) L.-L. Liu, J.-L. Yang and Y.-P. Shi, *J. Asian Nat. Prod. Res.*, 2011, **13**, 920–929; (c) J. J. Xu, N. H. Tan, J. Xiong, A. H. Adebayo, H. J. Han, G. Z. Zeng, C. J. Ji, Y. M. Zhang and M. J. Zhu, *Chin. Chem. Lett.*, 2009, **20**, 945–948; (d) J. Xu, J. Su, Y. Li and N. Tan, *Chem. Nat. Compd.*, 2013, **49**, 457–461; (e) P. Chen, P. P. Wang, Z. Z. Jiao and L. Xiang, *Helv. Chim. Acta*, 2014, **97**, 388–397; (f) J. Qu, S. Deng, L. Li, Y. Liu, Y. Li, S. Ma, X. Chen and S. Yu, *Phytochemistry*, 2016, **132**, 115–122; cyclohexenyl methyl ketone as an important building block for the total synthesis of natural products, see: (g) A. B. Smith III, J. R. Empfield, R. A. Rivero and H. A. Vaccaro, *J. Am. Chem. Soc.*, 1991, **113**, 4037–4038. β -Cyano ketones could be used to synthesize γ -amino acids, see: (h) M. Winkler, A. C. Knall, M. R. Kulterer and M. Klempier, *J. Org. Chem.*, 2007, **72**, 7423–7426; β -cyanoketone as an important building block in the synthesis of natural products and biologically active molecules, see: (i) A. Siwicka, D. Cuperly, L. Tedeschi, R. Le Vézouët, A. J. P. White and A. G. M. Barrett, *Tetrahedron*, 2007, **63**, 5903–5917; (j) H. Muratake and M. Natsume, *Tetrahedron*, 2006, **62**, 7071–7092; (k) L. N. Mander and R. J. Thomson, *J. Org. Chem.*, 2005, **70**, 1654–1670; (l) S. M. A. Rahman, H. Ohno, H. Yoshino, N. Satoh, M. Tsukaguchi, K. Murakami, C. Iwata, N. Maezaki and T. Tanaka, *Tetrahedron*, 2001, **57**, 127–134; (m) S. M. A. Rahman, H. Ohno, N. Maezaki, C. Iwata and T. Tanaka, *Org. Lett.*, 2000, **2**, 2893–2895.
- 18 (a) W.-B. Wu, X.-P. Zeng and J. Zhou, *J. Org. Chem.*, 2020, **85**, 14342–14350. For several related studies, see: (b) J.-J. Cao, F. Zhou and J. Zhou, *Angew. Chem., Int. Ed.*, 2010, **49**, 4976–4980; (c) X.-P. Zeng, Z.-Y. Cao, X. Wang, L. Chen, F. Zhou, F. Zhu, C.-H. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2016, **138**, 416–425.
- 19 See the ESI† for the possible formation pathway of two products.
- 20 F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, Wiley-Interscience, New York, 6th edn, 1992.
- 21 For selected reviews: (a) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602–1634; (b) J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001–1020; (c) D. Enders, C. Grondal and R. M. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–

1581; (d) K. C. Nicolaou and J. S. Chen, *Chem. Soc. Rev.*, 2009, **38**, 2993–3009; (e) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422–434. 22 (a) M. S. Newman and P. H. Goble, *J. Am. Chem. Soc.*, 1960, **82**, 4098–4099; (b) D. F. Taber and B. P. Gunn, *J. Org. Chem.*, 1979, **44**, 450–452; (c) P. G. Ciattini, E. Morera and G. Ortá, *Tetrahedron Lett.*, 1991, **32**, 6449–6452; (d)

M. E. Krafft, K. A. Seibert, T. F. N. Haxell and C. Hirose, *Chem. Commun.*, 2005, 5772–5774; (e) M. E. Krafft, T. F. N. Haxell, K. A. Seibert and K. A. Abboud, *J. Am. Chem. Soc.*, 2006, **128**, 4174–4175; (f) F.-F. Pan, P. Guo, C.-L. Li, P. Su and X.-Z. Shu, *Org. Lett.*, 2019, **21**, 3701–3705.