Catalytic synthesis of β-lactam derivatives by carbonylative cycloaddition of acylsilanes with imines via a palladium Fischer-carbene intermediate

Tetsuya Inagaki[1], Takuya Kodama [1,2] & Mamoru Tobisu [1,2] ✉

Fischer-type carbene complexes are characterized by the presence of a π-donating group, such as an alkoxy group on the carbene carbon. Despite the notable progress that has been made in synthetic methods that involve the use of Fischer-type carbene complexes, stoichiometric amounts of carbene complexes are still required for such reactions and catalytic variants remain elusive. This limitation primarily stems from the lack of suitable carbene precursors, which is in sharp contrast to the fact that carbene complexes bearing an electron-withdrawing group can be readily generated from the corresponding diazo esters. Here we report that acylsilanes can function as a precursor for a Fischer-carbene complex by the action of a palladium catalyst. This system can be used in catalytic carbonylative cycloaddition reactions with imines to form densely substituted β-lactam derivatives. A key siloxycarbene–palladium intermediate complex was isolated and successfully characterized by X-ray crystallography.

Since the first report in 1964 (ref. 1), Fischer-carbene complexes (FCs) have evolved into powerful reagents for organic synthesis, encompassing cycloaddition, carbene transfer and addition reactions of electrophiles and nucleophiles[2–5]. Although transformations enabled by FCs are unique, their use in catalytic reactions lags far behind from those involving metal carbene species bearing an electron-withdrawing group[6]. This is primarily because common diazo compounds cannot be used as precursors due to their instability of the corresponding heteroatom-substituted derivatives[7]. Therefore, FCs are typically accessed by the addition of organolithium (RLi) to a metal–carbonyl complex (M–CO) and the subsequent capture with an alkyl halide (R′X) (Fig. 1a)[2,4]. A few catalytic reactions that involve FCs have been reported so far, including the addition of heteroatom nucleophiles to vinylidene complexes[8–12], the substitution of Rh(II) carbenes bearing an iodonium leaving group by a tethered nucleophile[13], and the trapping of photochemically generated siloxycarbenes from acylsilanes with a Cu(I) catalyst[14,15]. However, the scope of these catalytic protocols for FCs remains limited, and the vast majority of intriguing transformations mediated by FCs requires the use of stoichiometric amounts of metal reagents. Among such transformations that are awaiting a catalytic protocol is the chromium FC-mediated synthesis of β-lactam derivatives, which proceed via the photo-induced carbonylation of an alkoxycarbene ligand to form a ketene, followed by a [2 + 2] cycloaddition with imines (Fig. 1b)[16–20].

We envisioned that this FC-mediated β-lactam synthesis might be conducted in a catalytic manner without photoirradiation based on a palladium/acylsilane reaction system (Fig. 1c). We previously reported on the palladium-catalysed siloxycyclopropanation of alkenes using acylsilanes, in which the oxidative addition of a C–Si bond triggers the in situ generation of a siloxycarbene–palladium

[1]Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Japan. [2]Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Suita, Japan. ✉e-mail: tobisu@chem.eng.osaka-u.ac.jp
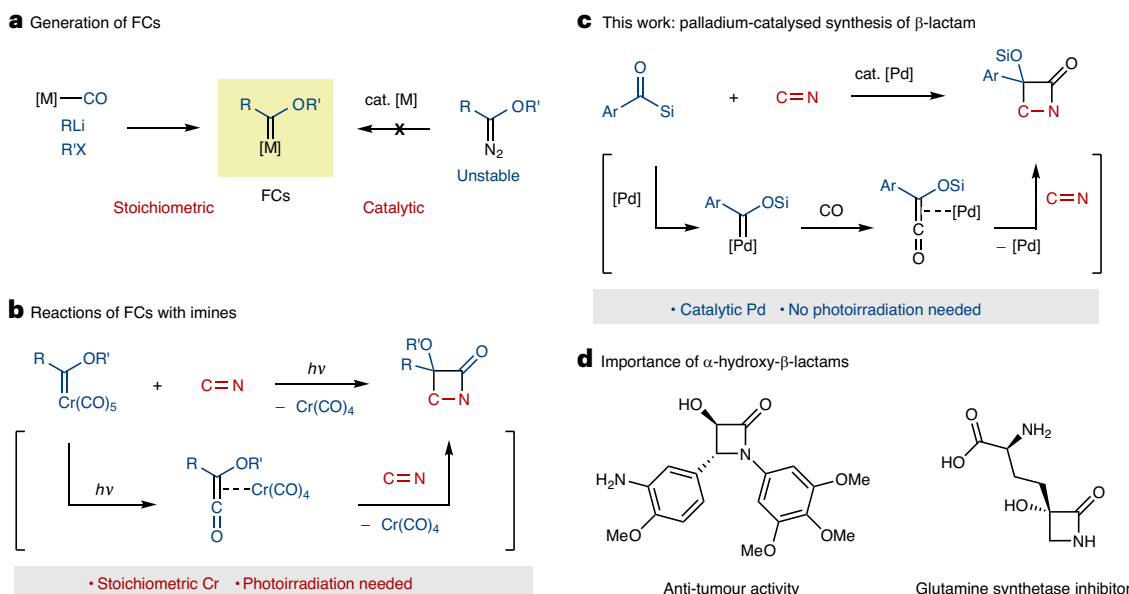
Fig. 1 | Background and the present study of FCs. a, Generation of FCs. **b**, Known stoichiometric reactions of FCs with imines. **c**, Palladium-catalysed carbonylative cycloaddition of acylsilanes with imines. **d**, Bioactive molecules containing α-hydroxy-β-lactams.

Table 1 | Pd-catalysed carbonylative annulation of acylsilane 1a and imine 2a

Entry	Deviation from entry 1	Yield (%)[a,b]		
		3aa	Recovered 2a	4
1	None	40 (4.3:1)	56	9
2	No CO	48 (4.2:1)	54	30
3	No CO with IPr* instead of IPr	93 (6.4:1)	5	65
4[c]	No palladium with IPr* instead of IPr	0	76	0
5[d]	No CO under dark conditions with IPr* instead of IPr	88 (6.4:1)	9	69

[a]**1a** (0.60 mmol), **2a** (0.20 mmol), Pd₂(dba)₃ (0.010 mmol), IPr (0.020 mmol) and toluene (0.60 ml) in COware at 110 °C for 17h. CO was generated from *p*-methoxyphenyl formate and Et₃N.
For details of COware, see Supplementary Tables 4–6. [b]Yields were determined by GC or NMR analysis. Stereoisomeric ratio is shown in the parentheses. [c]Run at 160 °C. [d]The reaction was performed in the absence of any light by covering the reaction vessel with aluminium foil.

intermediate[21]. If the thus generated siloxycarbene–palladium species would react with external CO to provide a ketene, this would lead to the formation of a β-lactam product without producing stoichiometric amounts of chromium waste or the need for photoirradiation[22,23]. The α-hydroxy-β-lactam skeleton[24–27] that would be made accessible by this catalytic method represents a major motif that is found in a variety of bioactive substances (Fig. 1d)[28]. In this Article, we describe that a palladium-mediated protocol for the generation of a siloxycarbene–palladium intermediate from acylsilanes can be applied to the catalytic synthesis of β-lactams.

An elusive siloxycarbene–palladium intermediate was isolated and characterized.

Results

Reaction development

Based on our previous studies on palladium-catalysed reactions of acylsilanes[21,29,30], we examined the reaction of the acylsilane **1a** (3.0 equiv.) and the imine **2a** in the presence of Pd₂(dba)₃ (10 mol% [Pd]), 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) (10 mol%) and CO (1.5 equiv.) in toluene at 110 °C, which afforded the expected
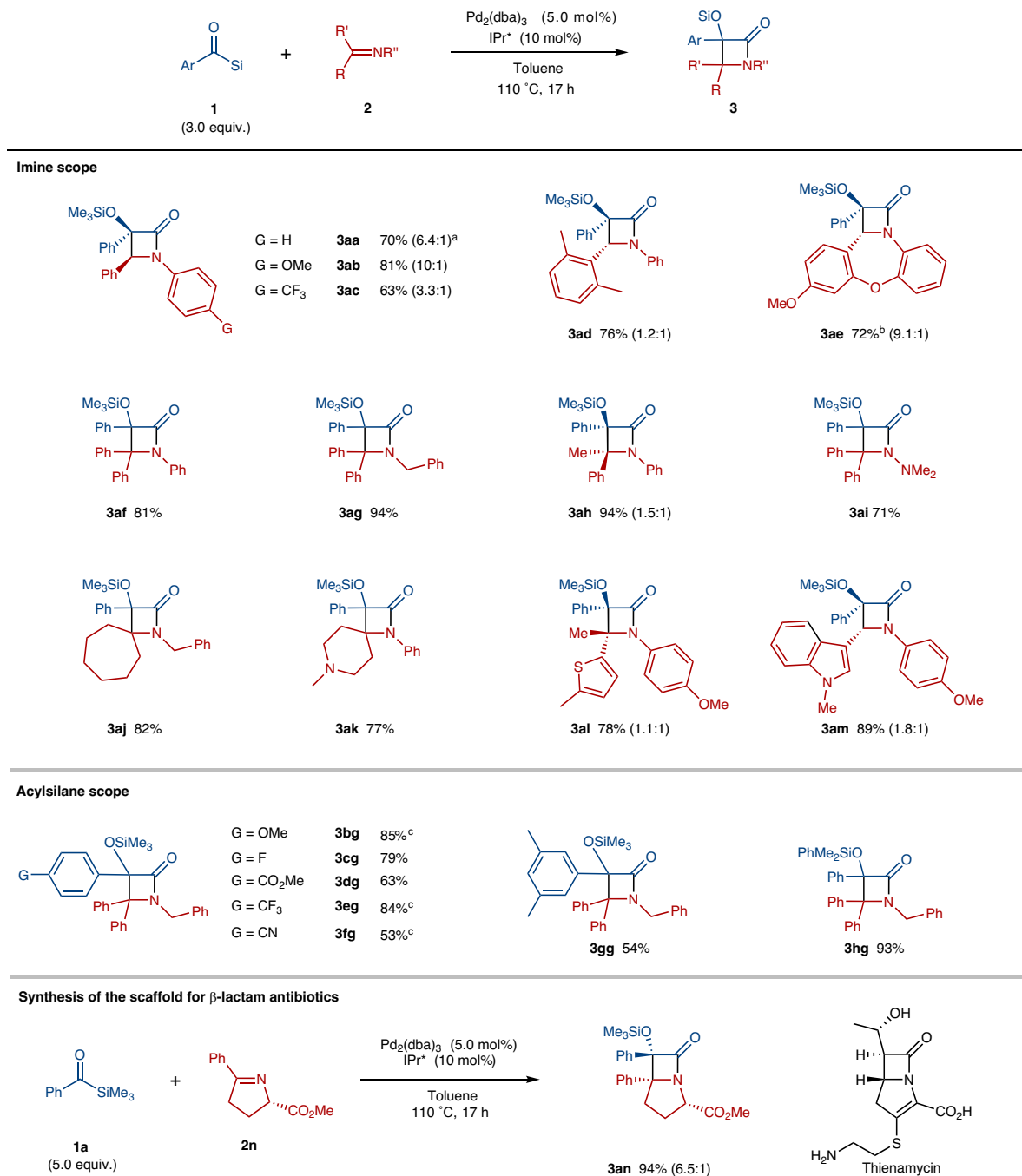
Fig. 2 | Scope of the palladium-catalysed synthesis of β-lactams by the reaction of acylsilanes and imines. Acylsilane (0.60 mmol), imine (0.20 mmol), Pd₂(dba)₃ (0.010 mmol), IPr* (0.020 mmol) and toluene (0.60 ml) in a sealed tube at 110 °C for 17 h. Isolated yields are shown. Ratios in parentheses are stereoisomer ratios, and the structure of the major isomer was determined by nuclear Overhauser effect spectroscopy. [a]The structure of the major isomer was determined by X-ray crystallography (Supplementary Fig. 4). [b]Acylsilane (1.0 mmol) was used. [c]Run at 160 °C.

β-lactam **3aa** in 40% yield (entry 1, Table 1). Interestingly, this reaction proceeded even in the absence of CO to furnish **3aa** in 48% yield (entry 2, Table 1). In this case, the phenylsilane **4**, which we assume was formed by the decarbonylation of **1a** (refs. 31–33), was also obtained in 30% yield. It therefore appears that palladium catalysis allows acylsilanes to serve not only as a carbene precursor but also as a source of CO, making this protocol operationally simple. The use of 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene (IPr*) substantially improved the yield of **3aa** to 93% (entry 3, Table 1). No reaction occurred in the absence of a palladium catalyst, excluding the possibility that IPr* functions as an organocatalyst (entry 4, Table 1).

This reaction proceeds in the absence of light, which excludes a mechanistic scenario involving the photo-induced isomerization of **1a** to metal-free siloxycarbene (entry 5, Table 1)[34,35] (for additional data for optimization, see Supplementary Tables 1–6).

This palladium-catalysed method allows the synthesis of a diverse range of complex β-lactams from readily available acylsilane and imine building blocks (Fig. 2). Imines bearing functional groups, such as methoxy (that is, **2b**), trifluoromethyl (that is, **2c**) on the aromatic rings successfully participated in this reaction with the corresponding β-lactams being formed. Imines with a bulky 2,6-xylyl group (that is, **2d**) were also applicable to this reaction. The cyclic
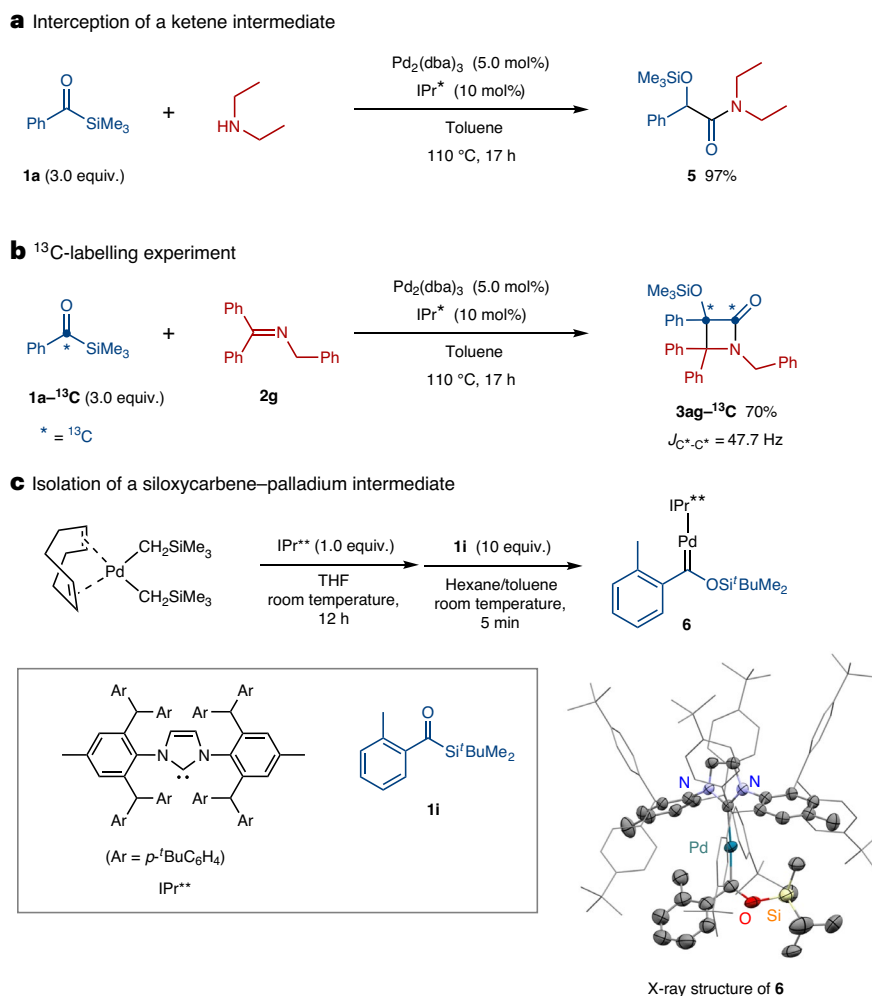
a Interception of a ketene intermediate

b ^{13}C-labelling experiment

c Isolation of a siloxycarbene–palladium intermediate

X-ray structure of **6**

Fig. 3 | Mechanistic studies. a, Interception of a ketene intermediate with diethylamine. **b**, A reaction using ^{13}C-labelled **1a**. **c**, Isolation of a siloxycarbene–palladium **6**. ORTEP drawing of **6** with thermal ellipsoids set at the 50% probability level is shown (for details, see Supplementary Fig. 5). THF, tetrahydrofuran.

imine **2e** served as a competent substrate, which allows access to complex polycyclic β-lactam skeleton (that is, **3ae**). Not only aldimines but also ketimines (that is, **2f**–**2l**) can be coupled successfully to form the corresponding β-lactams bearing contiguous quaternary stereocentres (that is, **3af**–**3al**). Regarding the nitrogen substituent on the imine substrates, aryl, benzyl and amino (that is, **2i**) groups were all compatible. Moreover, imines derived from cyclic ketones (that is, **2j** and **2k**) were transformed into spirocyclic β-lactams that are otherwise synthesized with difficulty (that is, **3aj** and **3ak**). Imines bearing heteroaryl groups, such as thiophene (that is, **2l**) and indole (that is, **2m**), were also applicable to this reaction. With respect to the acylsilane component, various benzoylsilane derivatives, including those bearing methoxy (**1b**), fluoride (**1c**), ester (**1d**), trifluoromethyl (**1e**), cyano (**1f**) and 3,5-xylyl (**1g**) groups, readily participated in this reaction. Acylsilanes bearing a PhMe$_2$Si group (that is, **1h**) can also be used successfully to form the corresponding β-lactam. This β-lactam synthesis is also applicable to the synthesis of a scaffold found in antibiotics. For example, the reaction of acylsilane **1a** with the cyclic imine **2n** furnished the bicyclic β-lactam **3an**, which possesses a molecular skeleton analogous to thienamycin. It should also be noted that a silyl group in the products obtained in this study can be removed by treatment with tetrabutylammonium fluoride to form the corresponding α-hydroxy-β-lactam derivative (for details, see Supplementary Methods).

Mechanistic studies

Some mechanistic studies were conducted to obtain insights into the reaction mechanism. The reaction of **1a** with diethylamine, instead of an imine, under the standard catalytic condition was found to afford the amide **5** in 97% yield (Fig. 3a). This observation supports the intermediacy of siloxyketene, which could be captured by diethylamine to form **5**. Second, the reaction of the ^{13}C-labelled acylsilane **1a**–^{13}**C** and the imine **2g** afforded the β-lactam **3ag**–^{13}**C**, in which C1 and C2 were both labelled, which is consistent with our mechanistic proposal that acylsilanes serve both as carbene and CO sources (Fig. 3b). Lastly, we successfully isolated a key siloxycarbene–palladium intermediate complex **6** by the reaction of Pd(CH$_2$SiMe$_3$)$_2$(cod), IPr** (1.0 equiv.)[36], and acylsilane **1i** (Fig. 3c). The structure of **6** was unambiguously determined by X-ray crystallography. It should be noted that complex **6** represents a sought-after isolated palladium complex bearing an alkoxycarbene ligand.

We also studied the mechanism for the generation of Pd–ketene complexes computationally using density functional theory (DFT) calculations at the ωB97XD/SDD-6-311+G*-SMD(toluene)//ωB97XD/LANL2DZ-6-31G*-SMD(toluene) level of theory (Fig. 4). Calculations were conducted using a model reaction of **1a** with a Pd-IPr complex. It was revealed that oxidative addition of the C(acyl)–Si bond in **1a** to the Pd–IPr complex proceeds through transition state **TS1** with a relatively low energetic barrier (8.5 kcal mol^{-1}), forming complex **INT2**. The silyl group **INT2** subsequently migrates to the oxygen atom of the
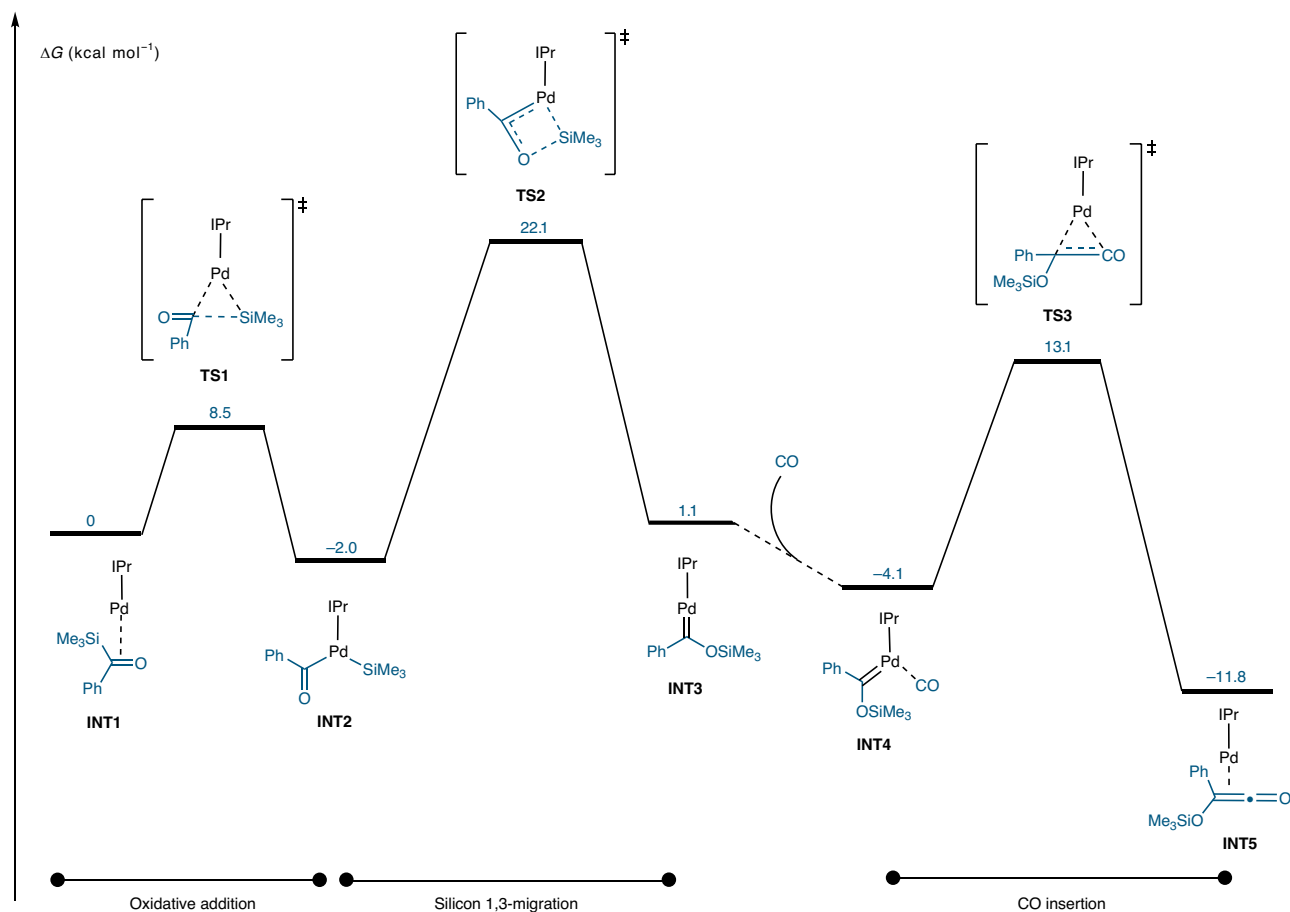
Fig. 4 | DFT calculations. Computed energy profiles of the generation pathways from Pd–acylsilane complex **INT1** to Pd–ketene complex **INT5** at the ωB97XD/SDD-6-311+G*-SMD(toluene)//ωB97XD/LANL2DZ-6-31G*-SMD(toluene) level of theory (for details, see Supplementary Fig. 1).

acyl ligand via the four-centred transition state **TS2** with a feasible activation barrier (24.1 kcal mol⁻¹), leading to carbene complex **INT3**. The coordination of CO, which is generated by a palladium-catalysed decarbonylation of **1a**, stabilizes **INT3** by 5.2 kcal mol⁻¹ to form **INT4**. **INT4** then undergoes CO insertion via **TS3** with a viable activation barrier (17.2 kcal mol⁻¹), generating the Pd–ketene complex **INT5** (for an energy profile of the reaction of **INT3** with **2a**, see Supplementary Figs. 2 and 3). DFT calculations of the following [2 + 2] cycloaddition reactions with imines were reported for related Cr and Pd–ketene complexes[37–39].

Conclusions

We report on the palladium-catalysed carbonylative cycloaddition of acylsilanes and imines, leading to the formation of densely functionalized β-lactam derivatives. Using this catalytic method, stoichiometric amounts of chromium–Fischer carbenes can be avoided. The key mechanistic feature of the reaction is the generation of a Fischer-type carbene complex from an acylsilane by a palladium/NHC catalyst, which was verified both experimentally and theoretically. The addition of external carbon monoxide, which is required for the formation of ketenes, is not necessary, because it is produced during the decarbonylation of acylsilanes, which is also catalysed by the same catalyst in the same reaction vessel. This operationally simple catalytic protocol allows for the rapid access to complex β-lactams from readily available building blocks. The system established in this study provides a reliable design principle in elusive Fischer-carbene catalysis. Further applications of this catalytic Fischer-carbene generation to other synthetic methods is currently ongoing in our laboratory.

Methods

A representative procedure for palladium-catalysed carbonylative cycloaddition of acylsilanes with imines

In a glovebox filled with nitrogen, Pd₂(dba)₃ (9.2 mg, 0.010 mmol), IPr* (18.3 mg, 0.020 mmol), acylsilane **1a** (107.0 mg, 0.6 mmol) and imine **2a** (37.3 mg, 0.21 mmol) were added to a 10-ml sample vial with a Teflon-sealed screwcap. Toluene (0.60 ml) was then added, and the vial was sealed with the cap. The vial was stirred at 110 °C for 17 h. After allowing the mixture to cool to room temperature, SiO₂ (Silica Gel 60 (spherical) NH₂) was added to the crude mixture, and the suspension was stirred at room temperature for 5 min. It was then filtered through a pad of SiO₂ (Silica Gel 60 (spherical) NH₂), and the pad was washed with EtOAc. The filtrate was concentrated in vacuo and purified by gel permeation chromatography (column: JAICEL-2HR-40, solvent: CHCl₃, flow rate: 25 ml min⁻¹) to give **3aa** as a white solid (55.9 mg, 70% yield).

Data availability

Experimental procedures and characterization data for all the catalytic and stoichiometric experiments along with computational information are included in Supplementary Information. Crystallographic data are available from the Cambridge Crystallographic Data Centre with the following codes: **Z-3aa** (2248876) and **6** (2255595). All other data are available from the corresponding author upon reasonable request.

References

1. Fischer, E. O. & Maasböl, A. On the existence of a tungsten carbonyl carbene complex. *Angew. Chem. Int. Ed.* **3**, 580–581 (1964).

2. de Meijere, A., Schirmer, H. & Duetsch, M. Fischer carbene complexes as chemical multitalents: the incredible range of products from carbenepentacarbonylmetal α,β-unsaturated complexes. *Angew. Chem. Int. Ed.* **39**, 3964–4002 (2000).

3. Gómez-Gallego, M., Mancheño, M. J. & Sierra, M. A. Catalytic transmetalation from group 6 Fischer carbene complexes: an emerging powerful tool in organic synthesis. *Acc. Chem. Res.* **38**, 44–53 (2005).

4. Dötz, K. H. & Stendel, J. Fischer carbene complexes in organic synthesis: metal-assisted and metal-templated reactions. *Chem. Rev.* **109**, 3227–3274 (2009).

5. Feliciano, A. et al. Fischer carbene complexes: a glance at two decades of research on higher-order cycloaddition reactions. *Chem. Eur. J.* **27**, 8233–8251 (2021).

6. Zhou, G., Guo, Z. & Shen, X. Electron-rich oxycarbenes: new synthetic and catalytic applications beyond group 6 Fischer carbene complexes. *Angew. Chem. Int. Ed.* **62**, e202217189 (2023).

7. Zhang, Z. & Wang, J. Recent studies on the reactions of α-diazocarbonyl compounds. *Tetrahedron* **64**, 6577–6605 (2008).

8. McDonald, F. E., Reddy, K. S. & Díaz, Y. Stereoselective glycosylations of a family of 6-deoxy-1,2-glycals generated by catalytic alkynol cycloisomerization. *J. Am. Chem. Soc.* **122**, 4304–4309 (2000).

9. Wipf, P. & Graham, T. H. Photoactivated tungsten hexacarbonyl-catalyzed conversion of alkynols to glycals. *J. Org. Chem.* **68**, 8798–8807 (2003).

10. Barluenga, J., Diéguez, A., Rodríguez, F. & Fañanás, F. J. Tandem [W(CO)₅]-catalyzed cycloisomerization–cyclopropanation reactions directed toward the synthesis of eight-membered carbocycles. *Angew. Chem. Int. Ed.* **44**, 126–128 (2005).

11. Takano, S., Shiomi, R., Morimoto, Y., Kochi, T. & Kakiuchi, F. Carbon–carbon bond formation via catalytically generated aminocarbene complexes: rhodium-catalyzed hydroaminative cyclization of enynes with secondary amines. *Angew. Chem. Int. Ed.* **59**, 11754–11757 (2020).

12. Morimoto, Y. et al. 2:1 versus 1:1 coupling of alkylacetylenes with secondary amines: selectivity switching in 8-quinolinolato rhodium catalysis. *Org. Lett.* **23**, 3803–3808 (2021).

13. Palomo, E. et al. Generating Fischer-type Rh-carbenes with Rh-carbynoids. *J. Am. Chem. Soc.* **145**, 4975–4981 (2023).

14. Takeuchi, T., Aoyama, T., Orihara, K., Ishida, K. & Kusama, H. Visible-light-induced in situ generation of Fischer-type copper carbene complexes from acylsilanes and its application to catalytic [4 + 1] cycloaddition with siloxydienes. *Org. Lett.* **23**, 9490–9494 (2021).

15. Zheng, L. et al. Cu/*Sa*Box-catalyzed photoinduced coupling of acylsilanes with alkynes. *Angew. Chem. Int. Ed.* **62**, e202216373 (2023).

16. McGuire, M. A. & Hegedus, L. S. Synthesis of β-lactams by the photolytic reaction of chromium carbene complexes with imines. *J. Am. Chem. Soc.* **104**, 5538–5540 (1982).

17. Hegedus, L. S., McGuire, M. A., Schultze, L. M., Yijun, C. & Anderson, O. P. Reaction of chromium carbene complexes with imines. Synthesis of β-lactams. *J. Am. Chem. Soc.* **106**, 2680–2687 (1984).

18. Hegedus, L. S., Schultze, L. M., Toro, J. & Yijun, C. Photolytic reaction of chromium and molybdenum carbene complexes with imines: synthesis of cepham, oxapenam, and oxacepham derivatives. *Tetrahedron* **41**, 5833–5838 (1985).

19. Hegedus, L. S., de Weck, G. & D'Andrea, S. Evidence for the intermediacy of chromium–ketene complexes in the synthesis of β-lactams by the photolytic reaction of chromium–carbene complexes with imines. Use in amino acid synthesis. *J. Am. Chem. Soc.* **110**, 2122–2126 (1988).

20. Sierra, M. A., Mancheño, M. J., Vicente, R. & Gòmez-Gallego, M. Synthesis of ferrocene-substituted 2-azetidinones. *J. Org. Chem.* **66**, 8920–8925 (2001).

21. Sakurai, S., Inagaki, T., Kodama, T., Yamanaka, M. & Tobisu, M. Palladium-catalyzed siloxycyclopropanation of alkenes using acylsilanes. *J. Am. Chem. Soc.* **144**, 1099–1105 (2022).

22. Zhang, Z., Zhang, Y. & Wang, J. Carbonylation of metal carbene with carbon monoxide: generation of ketene. *ACS Catal.* **1**, 1621–1630 (2011).

23. Roose, T. R. et al. Transition metal-catalysed carbene and nitrene transfer to carbon monoxide and isocyanides. *Chem. Soc. Rev.* **51**, 5842–5877 (2022).

24. Sun, L., Vasilevich, N. I., Fuselier, J. A., Hocart, S. J. & Coy, D. H. Examination of the 1,4-disubstituted azetidinone ring system as a template for combretastatin A-4 conformationally restricted analogue design. *Bioorg. Med. Chem. Lett.* **14**, 2041–2046 (2004).

25. Thomas, M. D., Langston-Unkefer, P. J., Uchytil, T. F. & Durbin, R. D. Inhibition of glutamine synthetase from pea by tabtoxinine-β-lactam. *Plant Physiol.* **71**, 912–915 (1983).

26. Cutrona, K. J. & Sanderson, P. E. J. The synthesis of thrombin inhibitor L-370,518 via an α-hydroxy-β-lactam. *Tetrahedron Lett.* **37**, 5045–5048 (1996).

27. Yang, Y., Wang, J. & Kayser, M. Approaches to the synthesis of enantiopure α-hydroxy-β-lactams with functionalized side chains. *Tetrahedron Asymmetry* **18**, 2021–2029 (2007).

28. Ye, J.-H., Bellotti, P., Paulisch, T. O., Daniliuc, C. G. & Glorius, F. Visible-light-induced cycloaddition of α-ketoacylsilanes with imines: facile access to β-lactams. *Angew. Chem. Int. Ed.* **60**, 13671–13676 (2021).

29. Inagaki, T., Sakurai, S., Yamanaka, M. & Tobisu, M. Palladium-catalyzed silylacylation of allenes using acylsilanes. *Angew. Chem. Int. Ed.* **61**, e202202387 (2022).

30. Inagaki, T., Ando, T., Sakurai, S., Yamanaka, M. & Tobisu, M. Palladium-catalyzed addition of acylsilanes across alkynes via the activation of a C–Si bond. *Chem. Sci.* **14**, 2706–2712 (2023).

31. Srimontree, W., Lakornwong, W. & Rueping, M. Nickel-catalyzed synthesis of silanes from silyl ketones. *Org. Lett.* **21**, 9330–9333 (2019).

32. Nakatani, S., Ito, Y., Sakurai, S., Kodama, T. & Tobisu, M. Nickel-catalyzed decarbonylation of acylsilanes. *J. Org. Chem.* **85**, 7588–7594 (2020).

33. Yoshida, T., Kodama, T. & Tobisu, M. Rhodium-catalyzed decarbonylation of acylsilanes. *Asian J. Org. Chem.* **11**, e202200610 (2022).

34. Zhang, H.-J., Priebbenow, D. L. & Bolm, C. Acylsilanes: valuable organosilicon reagents in organic synthesis. *Chem. Soc. Rev.* **42**, 8540–8571 (2013).

35. Priebbenow, D. L. Silicon-derived singlet nucleophilic carbene reagents in organic synthesis. *Adv. Synth. Catal.* **362**, 1927–1946 (2020).

36. Weber, S. G., Loos, C., Rominger, F. & Straub, B. F. Synthesis of an extremely sterically shielding *N*-heterocyclic carbene ligand. *ARKIVOC* **2012**, 226–242 (2012).

37. Arrieta, A. et al. A theoretical–experimental approach to the mechanism of the photocarbonylation of chromium(0) (Fischer)–carbene complexes and their reaction with imines. *J. Am. Chem. Soc.* **122**, 11509–11510 (2000).

38. Fernàndez, I., Sierra, M. A., Mancheño, M. J., Gòmez-Gallego, M. & Cossìo, F. P. Deeper insight into the mechanism of the reaction of photogenerated metallaketenes and imines. *J. Am. Chem. Soc.* **130**, 13892–13899 (2008).

39. Zhang, Z. et al. Pd-catalyzed carbonylation of diazo compounds at atmospheric pressure: a catalytic approach to ketenes. *J. Am. Chem. Soc.* **133**, 4330–4341 (2011).

Author contributions

T.I. and M.T. conceived the project. T.I. performed all the experimental and computational studies. T.K. performed X-ray crystallographic analysis. M.T. supervised the research. T.I. and M.T. prepared the initial paper. All authors reviewed and edited the paper.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41929-023-01081-5.

Correspondence and requests for materials should be addressed to Mamoru Tobisu.

Peer review information *Nature Catalysis* thanks Zhenghu Xu and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.