



Title	Native Amide-Directed C(sp ³) - H Amidation Enabled by Electron-Deficient RhIII Catalyst and Electron-Deficient 2-Pyridone Ligand
Author(s)	Wakikawa, Takumi; Sekine, Daichi; Murata, Yuta; Bunno, Youka; Kojima, Masahiro; Nagashima, Yuki; Tanaka, Ken; Yoshino, Tatsuhiko; Matsunaga, Shigeki
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Native Amide-Directed C(sp³)-H Amidation Enabled by Electron-Deficient Rh(III) Catalyst and Electron-Deficient 2-Pyridone Ligand

Takumi Wakikawa,^{†,[a]} Daichi Sekine,^{†,[a]} Yuta Murata,^[a] Youka Bunno,^[a] Masahiro Kojima,^[a] Yuki Nagashima,^[b] Ken Tanaka,^{*[b]} Tatsuhiko Yoshino,^{*[a,c]} and Shigeki Matsunaga^{*[a,c]}

[a] T. Wakikawa, D. Sekine, Y. Murata, Dr. Y. Bunno, Dr. M. Kojima, Dr. T. Yoshino, Prof. Dr. S. Matsunaga

Faculty of Pharmaceutical Sciences

Hokkaido University

Kita-ku, Sapporo 060-0812, Japan

E-mail: tyoshino@pharm.hokudai.ac.jp; smatsuna@pharm.hokudai.ac.jp

[b] Dr. Y. Nagashima, Prof. Dr. K. Tanaka

Department of Chemical Science and Engineering

Tokyo Institute of Technology

O-okayama, Meguro-ku, Tokyo 152-8550, Japan

E-mail: tanaka.k.cg@m.titech.ac.jp

[c] Dr. T. Yoshino, Prof. Dr. S. Matsunaga

Global Station for Biosurfaces and Drug Discovery

Hokkaido University

Kita-ku, Sapporo 060-0812, Japan

[†] Co-first authors; these authors contributed equally to this work.

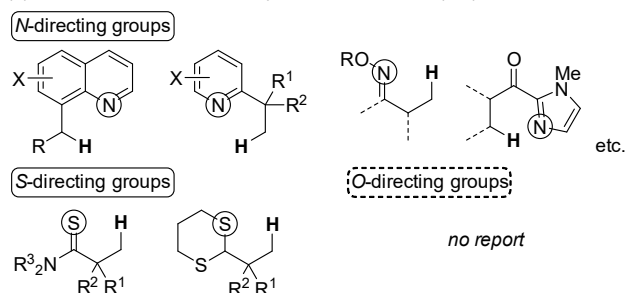
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Abstract: Trivalent group-9 metal catalysts with a cyclopentadienyl-type ligand (CpM^{III}; M = Co, Rh, Ir, Cp = cyclopentadienyl) have been widely used for directed C–H functionalizations, albeit that their application to challenging C(sp³)-H functionalizations suffers from the limitations of the available directing groups. In this report, we describe directed C(sp³)-H amidation reactions of simple amide substrates with a variety of substituents. The combination of an electron-deficient Cp^ERh catalyst (Cp^E = 1,3-bis(ethoxycarbonyl)-substituted Cp) and an electron-deficient 2-pyridone ligand is essential for high reactivity.

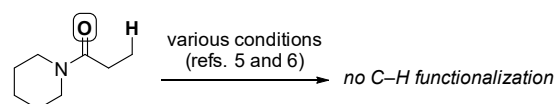
Direct functionalization reactions of inert C–H bonds of organic compounds have emerged as attractive methods for organic synthesis.^[1] To achieve selective and predictable functionalization at the desired site in the presence of many other C–H bonds, transition-metal-catalyzed C–H activation under the assistance of directing groups is a powerful strategy.^[1a] Among the various transition metals used for catalytic directed C–H activation reactions, trivalent group-9 metals with a cyclopentadienyl-type ligand (CpM^{III}; M = Co, Rh, Ir, Cp = cyclopentadienyl) are prominent due to their high reactivity and functional group tolerance.^[2] Since the seminal reports by Satoh and Miura in 2007,^[3] these catalysts have found numerous synthetic applications. However, the directed functionalization of C(sp³)-H bonds using CpM^{III} catalysts is less explored and relatively immature compared to C(sp²)-H functionalization.^[4–6] Particularly, the narrow scope of available directing groups is a major roadblock to further progress in this area (Scheme 1a); besides the functionalization of active allylic C–H bonds^[7] and outersphere C–H amidations via nitrene insertion,^[8] only strongly coordinating nitrogen-^[4] or sulfur-based^[5] directing groups have been successfully utilized for C(sp³)-H functionalization under CpM^{III} catalysis.

Amides are common, fundamental functional groups in organic chemistry, and C(sp³)-H functionalization reactions directed by the carbonyl oxygen atom of native amides are important for streamlined organic synthesis.^[9–11] However, the insufficient

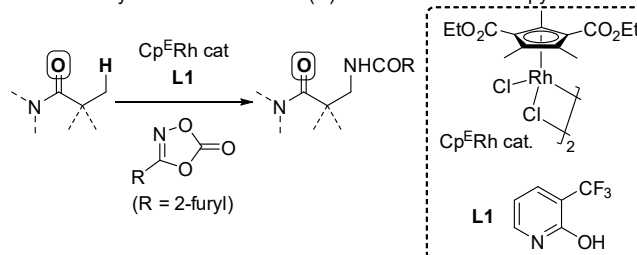
(a) Previous work: CpM^{III}-catalyzed *N/S*-directed C(sp³)-H functionalization



(b) Application of the previously reported conditions to a simple amide



(c) This work: Native amide-directed C(sp³)-H amidation enabled by electron-deficient Rh(III) + electron-deficient 2-pyridone



Scheme 1. CpM^{III}-catalyzed directed C(sp³)-H functionalization.

directing ability of non-anionic carbonyl oxygens of native amides renders such reactions challenging. Although Thioamides^[6a,b,d,e] and acylimidazoles^[5] have been employed as amide surrogates that undergo efficient directed C(sp³)-H functionalization reactions using Cp^{*}M^{III} catalysts (Cp^{*} = pentamethylcyclopentadienyl), the installation and transformation of the directing groups decrease the overall synthetic efficiency. So far, carbonyl-oxygen-directed C(sp³)-H functionalization reactions using CpM^{III} catalysts have not been realized. We subjected a simple amide to a variety of reaction conditions using a Cp^{*}M^{III} catalyst reported for C(sp³)-H functionalization reactions; unfortunately, none of the applied conditions delivered the desired products (Scheme 1b; for details, see the Supporting Information), indicating that much more efficient catalytic systems are required to enable native amide-directed C(sp³)-H functionalizations. It should also be noted here that while C(sp³)-H functionalizations directed by non-anionic native amide functionalities have been achieved using Pd(II)^[9,10] or Ir(I)^[11] catalysts, such studies have focused on the formation of C-C,^[9] C-O,^[10] and C-B^[11] bonds, while examples of the formation of C-N bonds remain scarce.^[12,13]

Here we report C(sp³)-H amidation reactions using an electron-deficient Cp^ERh^{III} catalyst (Cp^E = 1,3-bis(ethoxycarbonyl)-substituted Cp)^[14] in combination with an electron-deficient 2-pyridone ligand (Scheme 1c).^[15,16] The judiciously chosen Cp^ERh^{III}/2-pyridone combination is essential for high reactivity, and the optimized catalytic system enabled the β -selective amidation of a wide range of substrates with various substituents.

The introduction of electron-withdrawing groups into CpM^{III} catalysts can render them electron-deficient and thus alter their reactivity and selectivity.^[2d,14,17,18] Previous studies, including our own, revealed that such electron-deficient catalysts often exhibit much higher reactivity than conventional Cp^{*}M^{III} catalysts, which prompted us to examine the use of electron-deficient catalysts for challenging carbonyl-directed C(sp³)-H functionalization reactions. After extensive screening of the reaction conditions and catalytic additives to promote a C-H activation step via a concerted-metalation-deprotonation (CMD) or base-assisted-internal-electrophilic-substitution (BIES) mechanism,^[15,16,19] we found that the β -selective C(sp³)-H amidation of a propionamide derivative (**1a**) with a 2-furyl-substituted dioxazolone (**2a**)^[20] proceeded in 88% yield under the optimized conditions using [Cp^ERhCl₂]₂ and 3-trifluoromethyl-2-pyridone **L1** (for temperature and solvent effects, see Table S2 in the Supporting Information). The results under the optimal conditions and control experiments using other metal catalysts, ligands to assist C-H activation, and dioxazolones are summarized in Scheme 2. A highly electron-deficient [Cp^ERhCl₂]₂ catalyst exhibited the highest reactivity (88% yield), and [Cp^{*}CF₃RhCl₂]₂ afforded a moderate yield (57%), while the standard [Cp^{*}RhCl₂]₂ catalyst was the least reactive (5%) among the screened rhodium catalysts. The reactivity of the rhodium catalysts was related to their electron-deficiency. We also examined standard [Cp^{*}IrCl₂]₂ and [Cp^{*}CoCl₂]₂ catalysts, which failed to provide the desired product. We examined various 2-pyridone derivatives (**L1-L10**) as well as carboxylic acids (**L11, L12**) and carboxylate salts (**L13, L14**), as the ligand for C-H activation. While the 2-pyridones afforded the product in varying yields depending on their electronic and steric properties, the carboxylic acids and carboxylates scarcely promoted the reaction, indicating the superior reactivity of 2-pyridones over carboxylic acids for this challenging C(sp³)-H activation. Generally, electron-

deficient 2-pyridones (**L1-L3, L8**) were more effective than non-substituted (**L6**) or electron-rich derivatives (**L9, L10**),^[15] albeit that the introduction of a nitro group (**L5, L7**) resulted in somewhat poorer performance, possibly due to the coordination of the nitro group to the rhodium catalyst. 6-Trifluoromethyl-2-pyridone (**L4**) was unreactive, which might be attributed to steric effects. The

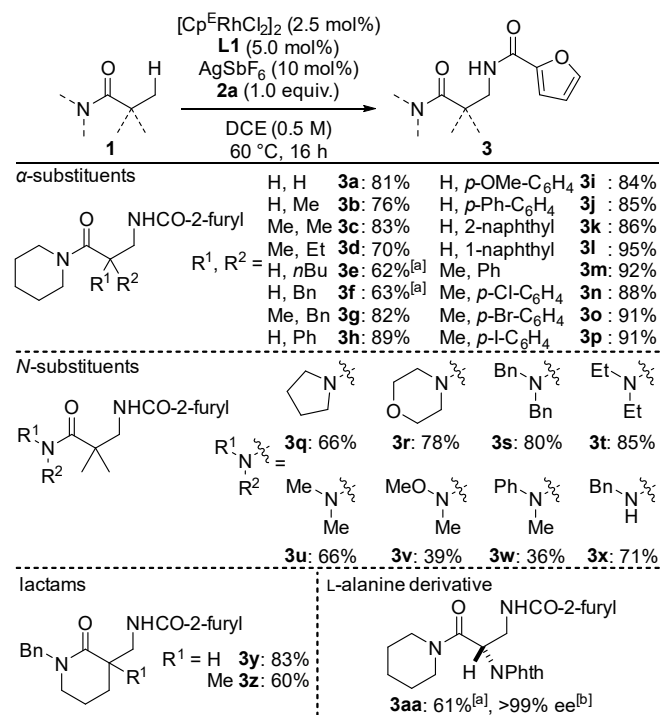
Scheme 2. Effects of varying metal catalysts, ligands that assist C-H activation, and dioxazolone **2** on the C(sp³)-H amidation of propionamide (**1a**). Reaction conditions: **1a** (0.05 mmol), **2** (0.05 mmol), metal catalyst (1.25 μ mol, 2.5 mol%), ligand (2.5 μ mol, 5 mol%), and AgSbF₆ (5.0 μ mol, 10 mol%) in DCE (0.1 mL) at 60 °C for 16 h. Yields of **3a** were determined by ¹H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard. N.D. = not detected. DCE = 1,2-dichloroethane.

results of these control experiments demonstrate that the combination of an electron-deficient rhodium catalyst and an electron-deficient 2-pyridone is key to the successful C(sp³)-H amidation reaction directed by a simple amide functionality. We also confirmed that the desired reaction did not proceed without

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any ligands. The structure of dioxazolone **2** also showed significant effects on the reactivity. While **2a** was the most reactive and 2-thienyl-substituted derivative **2b** exhibited moderate reactivity, phenyl- (**2c**) or alkyl-substituted dioxazolones (**2d**, **2e**) resulted in low yields.^[21]

Subsequently, we investigated the substrate scope under the optimal conditions using [Cp^FRhCl₂]₂ and **L1** (Scheme 3). First, substrates bearing various substituents at the α -position were

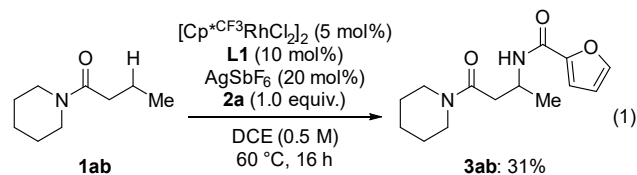


Scheme 3. Substrate scope of amide-directed C(sp³)-H amidation reactions. Reaction conditions: **1** (0.20 mmol), **2** (0.20 mmol), [Cp^FRhCl₂]₂ (5 μ mol, 2.5 mol%), **L1** (10 μ mol, 5 mol%), and AgSbF₆ (20 μ mol, 10 mol%) in DCE (0.4 mL) at 60 °C for 16 h. Isolated yields of **3** are given. Phth = phthaloyl. [a] [Cp^FRhCl₂]₂ (10 μ mol, 5 mol%), **L1** (20 μ mol, 10 mol%), and AgSbF₆ (40 μ mol, 20 mol%). [b] Enantiopure (>99%) **1aa** was used; ee determined by chiral HPLC analysis.

examined. Non-substituted (**3a**), mono-substituted (**3b**, **3e**, **3f**, **3h–3l**), and fully-substituted (**3c**, **3d**, **3g**, **3m–3p**) amides all underwent the C–H amidation at the β -position in good-to-high yield. It is noteworthy that the current protocol successfully afforded the desired product from a simple linear propionamide derivative (**3a**), which is unreactive in the previously reported Co(III)-catalyzed thioamide-directed C(sp³)-H amidation^[6a] probably due to the lack of Thorpe-Ingold effects to facilitate the formation of metallacycles via C–H activation. Next, we examined the effects of substituents on the nitrogen atom. Both cyclic (**3q**, **3r**) and acyclic (**3s–3w**) tertiary amides were tolerated under the optimized conditions to give the corresponding products. A Weinreb-amide (**3v**) and an *N*-methyl anilide (**3w**) exhibited somewhat diminished reactivity; nevertheless, the corresponding products were obtained in 39% and 36% yield, respectively. In addition to tertiary amides, a secondary amide underwent the C–H amidation in good yield (**3x**). Six-membered lactams were also applicable substrates (**3y**, **3z**). Finally, to further demonstrate the synthetic utility, we used an *N*-phthaloyl L-alanine derivative as a

substrate, and the desired C(sp³)-H amidation proceeded in 61% yield without racemization (**3aa**).^[22]

The feasibility of the more challenging methylene C(sp³)-H activation was examined using butylamide derivative **1ab** as a substrate (eq. 1). While the standard conditions using [Cp^FRhCl₂]₂ provided only a trace amount of the product, the combination of [Cp^{CF3}RhCl₂]₂ and **L1** afforded **3ab** in 31% yield. Although additional modifications and optimization of the catalyst and ligand would be required to achieve satisfactory reactivity, this preliminary result indicated the possibility of further expansion of the applicable substrates in future studies.



The reaction using amide **1m** as the substrate was carried out at the 1-mmol scale with a low catalyst loading (1 mol% based on Rh), and **3m** was isolated in 81% yield (Scheme 4a), demonstrating that the developed catalytic system is useful for a preparative-scale reaction. The 2-furoyl protecting group of **3a** can be easily removed by a two-step sequence of Boc-protection and hydrolysis under basic conditions (Scheme 4b).

We also investigated the kinetic isotope effect (KIE) in this reaction by comparing the initial reaction rates using **1a** or **1a-d₃** as the substrate. We observed a very large KIE ($k_H/k_D = 6.0$), which indicates that the C–H activation step is the rate-determining step of this reaction (Scheme 4c).

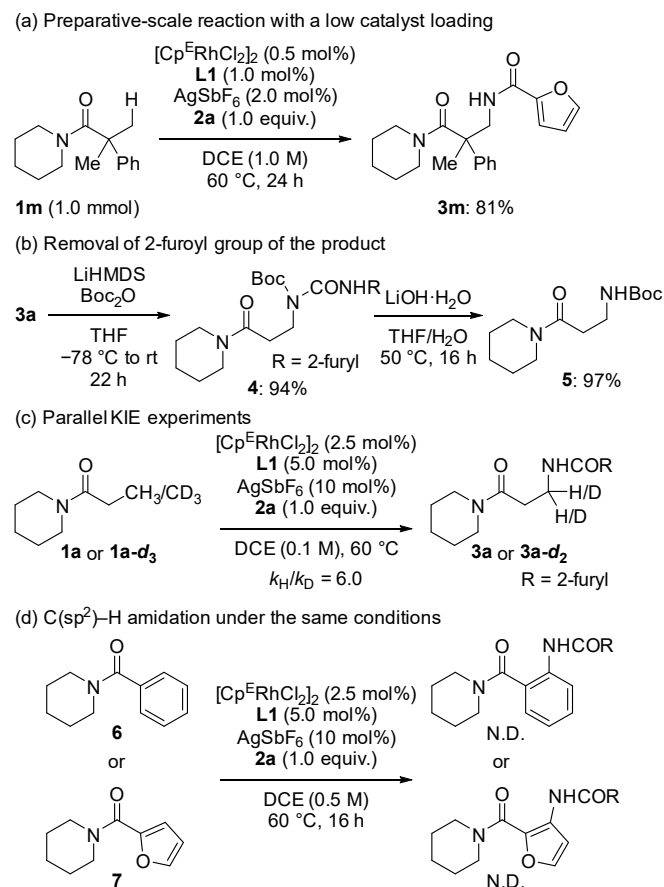
Finally, we checked whether the optimized catalytic system was applicable for C(sp²)-H amidation. Interestingly, neither benzamide **6** nor 2-furoyl amide **7** afforded the corresponding products under the optimized conditions (Scheme 4d), suggesting that the developed catalytic system is selective for C(sp³)-H amidations. This result is consistent with our observation that C(sp²)-H amidation of the 2-furoyl moiety of the amidated product **3** did not compete in any of the investigated cases. However, the reason for this selectivity is unclear at this point, and further mechanistic studies are necessary.

A plausible reaction mechanism, based on previous reports,^[6a,20] is shown in Figure 1. A [Cp^FRh] species with an **L1** in its anionic form would be generated from the Rh precursor, AgSbF₆, and **L1** to work as the catalytically active species (**I**). After the coordination of substrate **1** (**II**), C–H activation would proceed via a concerted mechanism to afford **III**. The observed large KIE clearly indicates that this step is the rate-determining step in the catalytic cycle. As suggested in previous studies of Pd-catalyzed reactions by Yu^[15] and Rh(III)-catalyzed reactions by Lu,^[16] 2-pyridone ligand **L1** might assist the C–H activation with its oxygen working as a base to facilitate the deprotonative C–H activation. The subsequent coordination of dioxazolone **2a** (**IV**) followed by formation of nitrene and its insertion into the Rh–C bond generates **V**. Finally, product **3** is liberated by protonation, accompanied by the regeneration of **I**.

In summary, we have demonstrated that the combination of an electron-deficient Cp^FRh^{III} catalyst and an electron-deficient 2-pyridone ligand (**L1**) enables amide-directed C(sp³)-H amidation reactions using dioxazolone **2a**. Native amide substrates with various substituents at the α -position as well as on the nitrogen atom provided the corresponding products in moderate-to-high

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yield. These findings may facilitate the further exploration of efficient catalytic systems for challenging but synthetically useful C(sp³)-H functionalization reactions based on CpM^{III} catalysts in future studies.



Scheme 4. Preparative-scale reaction; product transformation; KIE experiments; reactivity of aromatic amides **6** and **7**.

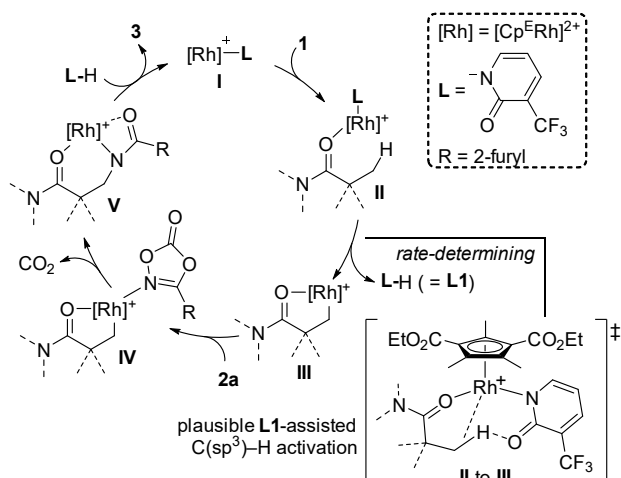


Figure 1. Plausible mechanism and L1-assisted C(sp³)-H activation.

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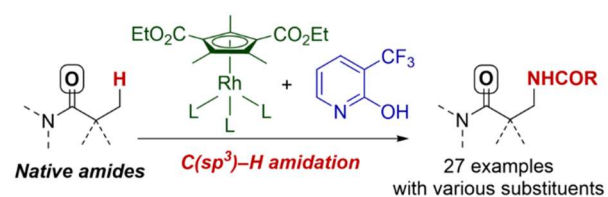
This work was supported in part by JSPS KAKENHI Grant Numbers JP19H00893 (K.T.), JP20H02730 (S.M.), JP21K05046 (T.Y.), and JP22H05346 (Y.N.) and JP22H05327 (T.Y.) in Transformative Research Areas (A) JP21A204 Digitalization-driven Transformative Organic Synthesis (Digi-TOS). This work was supported in part by Hokkaido University, Global Facility Center (GFC), Pharma Science Open Unit (PSOU), funded by MEXT under "Support Program for Implementation of New Equipment Sharing System".

Keywords: amide • C-H activation • dioxazolone • 2-pyridone • rhodium

- [1] a) C. Sambri, D. Schönbauer, R. Blicek, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603-6743; b) T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.* **2021**, *7*, 245-261; c) T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson, L. Ackermann, *Nat. Rev. Methods Primers* **2021**, *1*, 43.
- [2] a) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443-1460; b) T. Yoshino, S. Matsunaga, *Adv. Synth. Catal.* **2017**, *359*, 1245-1262; c) A. Peneau, C. Guillou, L. Chabaud, *Eur. J. Org. Chem.* **2018**, *2018*, 5777-5794; d) T. Piou, T. Rovis, *Acc. Chem. Res.* **2018**, *51*, 170-180; e) Y. Nishii, M. Miura, *ACS Catal.* **2020**, *10*, 9747-9757; f) S. Nunewar, S. Kumar, S. Talakola, S. Nanduri, V. Kanchupalli, *Chem. Asian J.* **2021**, *16*, 443-459.
- [3] a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407-1409; b) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362-5367.
- [4] a) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754-8786; b) B. Liu, A. M. Romine, C. Z. Rubel, K. M. Engle, B.-F. Shi, *Chem. Rev.* **2021**, *121*, 14957-15074.
- [5] For selected examples of nitrogen-directed reactions, see: a) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 4141-4144; b) N. Wang, R. Li, L. Li, S. Xu, H. Song, B. Wang, *J. Org. Chem.* **2014**, *79*, 5379-5385; c) X. Huang, Y. Wang, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2015**, *54*, 9404-9408; *Angew. Chem.* **2015**, *127*, 9536-9540; d) X. Wang, D.-G. Yu, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 10280-10283; *Angew. Chem.* **2015**, *127*, 10419-10422; e) H. Wang, G. Tang, X. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 13049-13052; *Angew. Chem.* **2015**, *127*, 13241-13244; f) M. Sen, B. Emayavaramban, N. Barsu, J. R. Premkumar, B. Sundararaju, *ACS Catal.* **2016**, *6*, 2792-2796; g) N. Barsu, M. A. Rahman, M. Sen, B. Sundararaju, *Chem. Eur. J.* **2016**, *22*, 9135-9138; h) S.-Y. Yan, P.-X. Ling, B.-F. Shi, *Adv. Synth. Catal.* **2017**, *359*, 2912-2917; i) R. Kumar, R. Kumar, D. Chandra, U. Sharma, *J. Org. Chem.* **2019**, *84*, 1542-1552; j) S. K. Mahato, N. Chatani, *ACS Catal.* **2020**, *10*, 5173-5178; k) E. Tan, M. Zanini, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2020**, *59*, 10470-10473; *Angew. Chem.* **2020**, *132*, 10556-10559; l) B. Liu, P. Xie, J. Zhao, J. Wang, M. Wang, Y. Jiang, J. Chang, X. Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 8396-8400; *Angew. Chem.* **2021**, *133*, 8477-8481; m) K. Antien, A. Geraci, M. Parmentier, O. Baudoin, *Angew. Chem. Int. Ed.* **2021**, *60*, 22948-22955; *Angew. Chem.* **2021**, *133*, 23130-23137. For other examples, see review 4b and references therein.
- [6] For examples of sulfur-directed reactions, see: a) P. W. Tan, A. M. Mak, M. B. Sullivan, D. J. Dixon, J. Seayad, *Angew. Chem. Int. Ed.* **2017**, *56*, 16550-16554; *Angew. Chem.* **2017**, *129*, 16777-16781; b) S. Fukagawa, Y. Kato, R. Tanaka, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2019**, *58*, 1153-1157; *Angew. Chem.* **2019**, *131*, 1165-1169; c) H. Shi, D. J. Dixon, *Chem. Sci.* **2019**, *10*, 3733-3737; d) R.-H. Liu, Q.-C. Shan, X.-H. Hu, T.-P. Loh, *Chem. Commun.* **2019**, *55*, 5519-5522; e) D. Sekine, K. Ikeda, S. Fukagawa, M. Kojima, T. Yoshino, S. Matsunaga, *Organometallics* **2019**, *38*, 3921-3926.

- [7] For selected examples of allylic C(sp³)-H functionalizations, see: a) T. Cochet, V. Bellosta, D. Roche, J.-Y. Ortholand, A. Greiner, J. Cossy, *Chem. Commun.* **2012**, 48, 10745-10747; b) Y. Shibata, E. Kudo, H. Sugiyama, H. Uekusa, K. Tanaka, *Organometallics* **2016**, 35, 1547-1552; c) A. Lerchen, T. Knecht, M. Koy, J. B. Ernst, K. Bergander, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, 57, 15248-15252; *Angew. Chem.* **2018**, 130, 15468-15472; d) H. Lei, T. Rovis, *J. Am. Chem. Soc.* **2019**, 141, 2268-2273; e) C. M. B. Farr, A. M. Kazerouni, B. Park, C. D. Poff, J. Won, K. R. Sharp, M.-H. Baik, S. B. Blakey, *J. Am. Chem. Soc.* **2020**, 142, 13996-14004.
- [8] a) S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M.-H. Baik, S. Chang, *Science* **2018**, 359, 1016-1021; b) J. Lee, S. Jin, D. Kim, S. H. Hong, S. Chang, *J. Am. Chem. Soc.* **2021**, 143, 5191-5200 and references therein.
- [9] a) H. Park, N. Chekshin, P.-X. Shen, J.-Q. Yu, *ACS Catal.* **2018**, 8, 9292-9297; b) R. Zhao, W. Lu, *Organometallics* **2018**, 37, 2188-2192; c) H. Park, Y. Li, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2019**, 58, 11424-11428; *Angew. Chem.* **2019**, 131, 11546-11550; d) H. Park, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, 142, 16552-16556; e) H.-Y. Hao, S.-J. Lou, S. Wang, K. Zhou, Q.-Z. Wu, Y.-J. Mao, Z.-Y. Xu, D.-Q. Xu, *Chem. Commun.* **2021**, 57, 8055-8058; f) L. Yang, H. Xie, G. An, G. Li, *J. Org. Chem.* **2021**, 86, 7872-7880.
- [10] a) L. Zhou, W. Lu, *Org. Lett.* **2014**, 16, 508-511; b) R. Zhao, W. Lu, *Org. Lett.* **2017**, 19, 1768-1771; c) Y. Xue, H. S. Park, C. Jiang, J.-Q. Yu, *ACS Catal.* **2021**, 11, 14188-14193.
- [11] a) Y. Shi, Q. Gao, S. Xu, *J. Am. Chem. Soc.* **2019**, 141, 10599-10604; b) Y. Yang, L. Chen, S. Xu, *Angew. Chem. Int. Ed.* **2021**, 60, 3524-3528; *Angew. Chem.* **2021**, 133, 3566-3570.
- [12] Monoanionic bidentate directing groups have been used for C(sp³)-H amidation and other functionalization reactions at the β- or γ-position. For details, see reviews: a) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, 120, 1788-1887; b) Zhang, Q.; Shi, B.-F. *Acc. Chem. Res.* **2021**, 54, 2750-2763.
- [13] Yu and co-workers reported the intramolecular C-H amidation of native amides assisted by bidentate coordination of an amide and a pendant carboxylate: S. Liu, Z. Zhuang, J. X. Qiao, K.-S. Yeung, S. Su, E. C. Cherney, Z. Ruan, W. R. Ewing, M. A. Poss, J.-Q. Yu, *J. Am. Chem. Soc.* **2021**, 143, 21657-21666.
- [14] Y. Shibata, K. Tanaka, *Angew. Chem. Int. Ed.* **2011**, 50, 10917-10921; *Angew. Chem.* **2011**, 123, 11109-11113.
- [15] For the use of 2-pyridone ligands for C-H activation under Pd catalysis, see: a) P. Wang, G.-C. Li, P. Jain, M. E. Farmer, J. He, P.-X. Shen, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, 138, 14092-14099; b) P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung, J.-Q. Yu, *Nature* **2017**, 551, 489-493; c) R.-Y. Zhu, Z.-Q. Li, H. S. Park, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, 140, 3564-3568; d) G. Xia, Z. Zhuang, L.-Y. Liu, S. L. Schreiber, B. Melillo, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2020**, 59, 7783-7787; *Angew. Chem.* **2020**, 132, 7857-7861; e) Z. Wang, L. Hu, N. Chekshin, Z. Zhuang, S. Qian, J. X. Qiao, J.-Q. Yu, *Science* **2021**, 374, 1281-1285 and references therein; see also ref. 13.
- [16] For the use of 2-pyridone ligands with a Cp*Rh(III) catalyst, see: P. Zhang, W. Chang, Y.-S. Kang, W. Zhao, P.-P. Cui, Y. Liang, W.-Y. Sun, Y. Lu, *Org. Lett.* **2020**, 22, 9462-9467.
- [17] For electron-deficient Rh(III) catalysts and their applications, see: a) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2014**, 136, 2735-2738; b) Y. Hoshino, Y. Shibata, K. Tanaka, *Adv. Synth. Catal.* **2014**, 356, 1577-1585; c) F. Romanov-Michailidis, K. F. Sedillo, J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2015**, 137, 8892-8895; d) Y. Takahama, Y. Shibata, K. Tanaka, *Chem. Eur. J.* **2015**, 21, 9053-9056; e) T. Piou, F. Romanov-Michailidis, M. Romanova-Michaelides, K. E. Jackson, N. Semakul, T. D. Taggart, B. S. Newell, C. D. Rithner, R. S. Paton, T. Rovis, *J. Am. Chem. Soc.* **2017**, 139, 1296-1310; f) S. Yoshizaki, Y. Shibata, K. Tanaka, *Angew. Chem. Int. Ed.* **2017**, 56, 3590-3593; *Angew. Chem.* **2017**, 129, 3644-3647; g) E. J. T. Phipps, T. Rovis, *J. Am. Chem. Soc.* **2019**, 141, 6807-6811; h) R. Yoshimura, Y. Shibata, T. Yamada, K. Tanaka, *J. Org. Chem.* **2019**, 84, 2501-2511; h) R. Yoshimura, Y. Shibata, K. Tanaka, *J. Org. Chem.* **2019**, 84, 13164-13171; i) J. Tanaka, Y. Shibata, A. Joseph, J. Nogami, J. Terasawa, R. Yoshimura, K. Tanaka, *Chem. Eur. J.* **2020**, 26, 5774-5779; j) Y. Nagashima, S. Ishigaki, J. Tanaka, K. Tanaka, *ACS Catal.* **2021**, 11, 13591-13602; k) J. Tanaka, Y. Nagashima, A. J. Araujo Dias, K. Tanaka, *J. Am. Chem. Soc.* **2021**, 143, 11325-11331; see also ref. 14.
- [18] For electron-deficient Ir(III) catalysts and their applications, see: a) F. Romanov-Michailidis, B. D. Ravetz, D. W. Paley, T. Rovis, *J. Am. Chem. Soc.* **2018**, 140, 5370-5374; b) H. Lei, J. H. Conway, Jr., C. C. Cook, T. Rovis, *J. Am. Chem. Soc.* **2019**, 141, 11864-11869; c) E. Tomita, K. Yamada, Y. Shibata, K. Tanaka, M. Kojima, T. Yoshino, S. Matsunaga, *Angew. Chem. Int. Ed.* **2020**, 59, 10474-10478; *Angew. Chem.* **2020**, 132, 10560-10564.
- [19] a) D. L. Davies, S. A. Macgregor, C. L. McMullin, *Chem. Rev.* **2017**, 117, 8649-8709; b) R. A. Alharis, C. L. McMullin, D. L. Davies, K. Singh, S. A. Macgregor, *J. Am. Chem. Soc.* **2019**, 141, 8896-8906 and references therein.
- [20] a) Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, 137, 4534-4542; b) K. M. van Vliet, B. de Bruin, *ACS Catal.* **2020**, 10, 4751-4769.
- [21] *tert*-Butyl (pivaloyloxy)carbamate (PivO-NHBoc) was also examined as an electrophilic aminating reagent, but the desired reaction did not proceed. For the use of related reagents for C-H amination reactions, see: a) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2013**, 15, 3014-3017; b) P. Patel, S. Chang, *ACS Catal.* **2015**, 5, 853-858.
- [22] The corresponding *N*-Boc- or *N*-Cbz-protected alanine derivatives failed to afford the C-H amidation products probably due to the competitive coordination of the carbamate moiety.

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Direct $\text{C}(\text{sp}^3)\text{-H}$ functionalization reactions of native amides can facilitate streamlined synthesis of valuable molecules, but their insufficient directing ability is one of the current severe challenges of the field. Here we report that the combination of an electron-deficient Rh(III) catalyst and an electron-deficient 2-pyridone ligand shows high catalytic activity for $\text{C}(\text{sp}^3)\text{-H}$ amidation of various native amides.

Institute and/or researcher Twitter usernames: @tokyotech_en @KenTanaka_Lab @HokkaidoUni @MatsunagaGroup