Rh-catalyzed regiodivergent hydrosilylation of acyl aminocyclopropanes controlled by monophosphine ligands†

Hiroki Kondo,a Kenichiro Itamiab and Junichiro Yamaguchic*

A Rh-catalyzed regiodivergent hydrosilylation of acyl aminocyclopropanes has been developed. Acyl aminocyclopropanes were reacted with hydrosilanes in the presence of Rh catalysts to afford ring-opened hydrosilylated adducts through carbon–carbon (C–C) bond cleavage of the cyclopropane ring. The regioselectivity of the addition of silanes (linear or branched) can be switched by changing the monophosphine ligand. This C–C bond cleavage/hydrosilylation methodology is applicable to the synthesis of silanediol precursors.

Introduction

Catalytic carbon–carbon (C–C) bond activation can be an efficient way to create valuable bonds from readily available starting materials. The development of methodologies for both the breaking of C–C bonds and the forming of new C–C and C–heteroatom bonds enables the synthesis of complex organic molecules in a novel and more efficient manner. In previous studies of transition-metal catalyzed C–C bond cleavage reactions, strained molecules have usually been employed. Particularly, cyclopropanes have been well investigated due to their high reactivity derived from a high strain energy. Various types of ring-opening reactions of “activated” cyclopropanes such as alkyldieneacylcyclopropanes and donor–acceptor cyclopropanes have been reported, enabling the construction of diverse frameworks. However, mono-substituted cyclopropanes, which have inert C–C bonds compared to the “activated” cyclopropanes described above, are still difficult to functionize and have limited application in organic synthesis. Since mono-substituted cyclopropanes such as cyclopropylamine are readily available (85 per gram from Sigma-Aldrich), its synthetic utility might be enhanced if it can be coaxed into a new C–C bond activation mode. Recently, the Bower group reported excellent examples for a C–C activation/alkene formation sequence using acyl aminocyclopropanes.6,7

Hydrosilylation is a classical and well-studied reaction, particularly for double bonds such as alkenes, alkynes, ketones, and imines under transition-metal catalysis. However, regarding the hydrosilylation of C–C single bonds, only a narrow scope of selected cyclopropanes has been studied. Catalytic hydrosilylation of “activated” cyclopropanes is known, and the site-selectivity of the C–C bond cleavage depends on the substituents on both the substrate and the catalyst (Scheme 1A).6,7 Specifically, the catalytic hydrosilylation of mono-substituted cyclopropanes has only been demonstrated in one report. In a related literature precedent, the

Scheme 1 Transition-metal catalyzed hydrosilylation of cyclopropanes via C–C bond activation.
Chirik group reported a two-step catalytic hydrosilylation of cyclopropyl alcohol in the presence of Wilkinson's catalyst (Scheme 1B). They discovered that the proximal bond (C(α)–C(β) bond) of the cyclopropane can be cleaved selectively under the influence of the Rh catalyst by using PPh3 as a directing group, followed by hydrosilylation of the alkene to give the resulting alkylsilane.

During our efforts to develop C–H functionalization of aminocyclopropanes, we serendipitously discovered a Rh-catalyzed hydrosilylation of acyl aminocyclopropanes via C–C bond cleavage (Scheme 1C). We have found that the regioselectivity of the addition of silanes can be controlled by changing the monophosphine ligand to give linear or branched alkylsilanes.

To the best of our knowledge, switching the regioselectivity by ligand control in a catalytic hydrosilylation of mono-substituted cyclopropanes has not been reported thus far. Additionally, since the functional motif of the resulting α-aminosilane is known to exhibit biological activity and is a prominent feature in silanediol protease inhibitors (Scheme 1D), many strategies for its preparation have been reported.

This hydrosilylation methodology would introduce various silyl groups in an atom-economical fashion without the use of organometallic reagents.

**Results and discussion**

At the outset of our studies, we chose cyclopropylamine 1A and silane 2a as model substrates (Table 1). To our delight, hydrosilylated product 3Aa, which was formed through C(a)–C(b) bond cleavage and addition of the silyl group to the terminal carbon C(γ), was obtained in 40% yield with 2.5 mol% [Rh(cod)Cl]2 in THF at 120 °C for 6 h (Table 1, entry 1).

When examining ligand effects, we observed that 1,10-phenanthroline (phen), which is a bidentate nitrogen ligand, is ineffective (entry 2). When 1,4-bis(diphenylphosphino)butane (dpbb) was employed, a mixture of linear product 3Aa and branched product 4Aa was obtained (entry 3). The monodentate phosphine ligand PCy3 provided 3Aa as the major product (entry 4). Moreover, when a more electron-rich and bulky ligand, PCy3, was used, regioselective hydrosilylation proceeded to yield the linear 3Aa in higher yield (56% isolated yield, entry 5). On the other hand, when PPh3 and tri(naphthalen-1-yl)phosphine [P(1-nap)]3 were used as ligands, the regioselectivity dramatically changed: branched product 4Aa, which has a silyl group at the α position to the nitrogen, was obtained in high yields (entries 6 and 7). In this manner, we accomplished a switching of the regioselectivity when reacting cyclopropylamine 1A with hydrosilane 2a via C–C bond cleavage solely by changing the ligand on the Rh catalyst.

![Scheme 2 Scope of cyclopropamines and hydrosilanes in the hydrosilylation by a Rh/P(1-nap)3 catalyst.](image-url)

**Table 1** Investigation of the ligand effect in a Rh-catalyzed hydrosilylation of cyclopropylamine 1A

| Entry | Ligand | 3Aa (%) | 4Aa (%) |
|-------|--------|---------|---------|
| 1     | None   | 40      | <1      |
| 2     | Phen   | <1      | <1      |
| 3     | dpbb   | 10      | 25      |
| 4     | PCy3Ph | 42      | 6       |
| 5     | PCy3   | 61 (56) | <1      |
| 6     | PPh3   | 17      | 83      |
| 7     | P(1-nap)3 | 92 (81) |         |

*Conditions: 1A (0.35 mmol), 2a (2.0 equiv.), [Rh(cod)Cl]2 (2.5 mol%), ligand (bidentate: 5 mol%, monodentate: 10 mol%), THF (2.0 mL), 120 °C, 6 h. *Yields were determined by 1H NMR analysis of the crude product using CH2Br2 as an internal standard. *Isolated yield. *PCy3, HBF4 was used as the precursor.
With optimized reaction conditions in hand, we evaluated the scope of cyclopropylamines and silanes under the \([\text{Rh(cod)Cl}]_2/\text{P(1-nap)}_3\) catalytic system (Scheme 2).

Cyclopropanes bearing cyclohexyl, isopropyl and tetrahydropyranyl groups were applicable in this reaction (\(4\text{Ba–4Fa}\)). Even carbamate \(1\text{G}\) performed well to give the corresponding product \(4\text{Ga}\) in 69% yield. Aminocyclopropanes protected by various benzoyl groups were tolerated to produce the desired products in good yields (\(4\text{Ha–4Na}\)). Cyclopropylamines with heteroaromatic substituents such as pyridine and furan rings were tolerated under the reaction conditions to afford hydrosilylated adducts in moderate yields (\(4\text{Oa–4Qa}\)). Probenecid derivative \(1\text{R}\) could be transformed to alkylsilane \(4\text{Ra}\). Valine derivative \(1\text{S}\) and proline derivative \(1\text{T}\) can also be applied to this reaction, furnishing \(4\text{Sa}\) and \(4\text{Ta}\) in moderate yields.

Various trialkylsilanes \(1\text{b–1e}\) were also applicable and gave the corresponding hydrosilylated products in moderate to excellent yields (\(4\text{Ab–4Ae}\)). Typically, the regioselectivity of branched:linear products was in the range of 10 : 1 to 3 : 1.\(^{13}\)

Next, the substrate scope of aminocyclopropanes in the \([\text{Rh(cod)Cl}]_2/\text{PCy}_3\cdot\text{HBF}_4\) catalytic system was examined (Scheme 3).

The reaction of cyclopropylamines bearing various acyl protecting groups proceeded smoothly with virtually complete regioselectivities to provide the corresponding linear products (\(3\text{Aa}, 3\text{Ba}, 3\text{Ma}, 3\text{Na}, 3\text{Ua}, \text{and } 3\text{Va}\)) in moderate yields.\(^{14}\)

To demonstrate the synthetic applicability of the linear product, alkylsilane \(3\text{Ma}\) was converted to the corresponding alcohol \(5\text{Ma}\) by treatment with \(\text{Bu}_4\text{NF}/\text{H}_2\text{O}_2/\text{KHCO}_3\) in \(\text{THF}/\text{MeOH}\) (Scheme 4).\(^{15}\) In this manner, this hydrosilylation methodology can give access to a versatile building block for further transformation.

To gain insight into the reaction mechanism, several experiments were conducted (Scheme 5). Firstly, we tried to isolate the reaction intermediates. Gratifyingly, hydrosilylated product \(4\text{Ab}\) as well as \((E)\)- and \((Z)\)-enamide \(6\text{A}\) were isolated when the reaction of \(1\text{A}\) with tert-butyldimethylsilane (\(2\text{b}\)) in the presence of \([\text{Rh(cod)Cl}]_2/\text{P(1-nap)}_3\) was terminated at only 3 h of reaction time (Scheme 5A). This result indicated that the C–C bond cleavage generates the corresponding olefins in situ. Next, the reaction intermediates were subjected to our standard conditions (Scheme 5B). When \((E)\)-\(6\text{A}\) and \((Z)\)-\(6\text{A}\) were reacted with silane \(2\text{a}\) by using \(\text{P(1-nap)}_3\) as the ligand, the branched \(4\text{Aa}\) was obtained in 80% yield. This result is consistent with that of the hydrosilylation of \(1\text{A}\) (Table 1, entry 7).\(^{16}\) On the other hand, when \(\text{PCy}_3\cdot\text{HBF}_4\) was employed, the hydrosilylated products did not form.\(^{12}\) Additionally, when we subjected allylamine \(7\text{A}\), which is another possible intermediate, under the same reaction conditions,\(^{17}\) \(3\text{Aa}\) was obtained in 21% yield along with 41% yield of \(4\text{Aa}\). This suggested that the isomerization of the olefin took place in situ. On the other hand, the hydrosilylation

\[\text{Scheme 3} \quad \text{Scope of cyclopropylamines in the hydrosilylation by a Rh/PCy}_3\cdot\text{HBF}_4\text{ catalyst.}^{4} \quad \text{aIsolated yields.} \quad \text{b12 h.} \quad \text{c25 h.} \quad [\text{Si}] = \text{SiMe(OSiMe}_3)_2.\]

\[\text{Scheme 4} \quad \text{Tamao oxidation of aminosilane 3Ma.}\]

\[\text{Scheme 5} \quad \text{Mechanistic exploration.} \quad \text{aIsolated yields.} \quad \text{bYields were determined by}^{1} \text{H NMR analysis of the crude product using CH}_2\text{Br}_2\text{ as an internal standard.}\]
of 7A using PCy₃-HBF₄ afforded the linear product 3Aa with high regioselectivity.²²

According to our observations, a possible reaction mechanism is depicted (Scheme 5C). First, oxidative addition of the C(α)-C(β) bond to the Rh(i) catalyst occurs to generate rhoda-

bly. Allylamine E and enamide F could be formed via β-H elimination, followed by reductive elimination from C and D. Both E and F would exist in equilibrium through intermediate G. Subsequently, Rh-catalyzed hydrosilylation of E or F would proceed by a modified Chalk–Harrod mechanism, giving H and I.¹⁸ Finally, a reductive elimination step yields 3 and 4 as the products.

Although the ligand effect remains unclear, we propose the following explanation: when PCy₃ is used as the ligand, an electron-rich Rh complex with a high reduction ability is formed. Thus, enamides and imines, generated by isomerization, are hydrogenated immediately. This undesired pathway competes with the formation of the branched 4, leading to the high regioselectivity of the linear 3. On the other hand, enamide 6A was selectively formed in the reaction of allylamine 7A under [Rh(cod)Cl₂][P(1-nap)] catalytic conditions.¹⁸ This result suggests that P(1-nap)₃ is promoting the isomerization of allylalmine to enamides. Furthermore, the regioselectivity might be correlated to the cone angle of the ligands (Fig. 1).²⁰ Ligands with larger cone angles favor the linear product 3Aa, whereas ones with smaller cone angles tend to produce branched product 4Aa. Also, the IR stretching frequency of the Ni(CO)₃(L) (L = ligand) catalysts did not show any relationship between the regioselectivity and the electronic cis effect of the phosphines.²⁰ These factors suggest that the bulkiness of the ligand suppresses the hydrosilylation of the more sterically hindered enamide 6A compared to allylamine 7A.

Conclusions

We have successfully developed a ligand-controlled, Rh-catalyzed regiodivergent hydrosilylation of acyl aminocyclopropanes with a wide range of silanes. Initial mechanistic investigations suggest that selective C-C bond cleavage takes place to generate allyl-

amine and enamides, which are hydrosilylated by the Rh catalyst. Precise elucidation of ligand effects and application to asymmetric hydrosilylation are ongoing in our laboratory.

Acknowledgements

This work was supported by JSPS KAKENHI Grant No. JP16H01011 and JP16H01414 (to J. Y.), the ERATO program from JST (K. I.), and a JSPS research fellowship for young scientists (to H. K.). ITbM is supported by the World Premier International Research Center (WPI) Initiative, Japan.

Notes and references

1 (a) W. D. Jones, Nature, 1993, 364, 676; (b) M. Murakami and Y. Ito, Top. Organomet. Chem., 1999, 3, 97; (c) B. Rybtchinski and D. Milstein, Angew. Chem., Int. Ed., 1999, 38, 870; (d) C. Perthusiot, B. L. Edelbach, D. L. Zubris, N. Sinhai, C. N. Iverson, C. Müller, T. Satoh and W. D. Jones, J. Mol. Catal. A: Chem., 2002, 189, 157; (e) M. E. van der Boom and D. Milstein, Chem. Rev., 2003, 103, 1759; (f) C.-H. Jun, Chem. Soc. Rev., 2004, 33, 610; (g) T. Satoh and M. Miura, Top. Organomet. Chem., 2005, 14, 1; (h) T. Kondo and T. Mitsudo, Chem. Lett., 2005, 34, 1462; (i) C.-H. Jun and J. W. Park, Top. Organomet. Chem., 2007, 24, 117; (j) D. Necas and M. Kotora, Curr. Org. Chem., 2007, 11, 1566; (k) Y. J. Park, J.-W. Park and C.-H. Jun, Acc. Chem. Res., 2008, 41, 222; (l) H. Yorimitsu and K. Oshima, Bull. Chem. Soc. Jpn., 2009, 82, 778; (m) M. Murakami and T. Matsuda, Chem. Commun., 2011, 47, 1100; (n) A. Dermenci, J. W. Coe and G. Dong, Org. Chem. Front., 2014, 1, 567; (o) F. Chen, T. Wang and N. Jiao, Chem. Rev., 2014, 114, 8613; (p) L. Souillart and N. Cramer, Chem. Rev., 2015, 115, 9410; (q) M. E. O’Reilly, S. Dutta and A. S. Veige, Chem. Rev., 2016, 116, 8105; (r) Y. Xia, G. Lu, P. Liu and G. Dong, Nature, 2016, 539, 546; (s) C–C Bond Activation, ed. G. Dong, Springer, 2014; (t) G. Fumagalli, S. Stanton and J. F. Bower, Chem. Rev., 2017, DOI: 10.1021/acs.chemrev.6b00599.

2 For reviews for cyclopropanes, see: (a) I. Nakamura and Y. Yamamoto, Adv. Synth. Catal., 2002, 344, 111; (b) H.-U. Reissig and R. Zimmer, Chem. Rev., 2003, 103, 1151; (c) A. Masarwa and I. Marek, Chem.–Eur. J., 2010, 16, 9712; (d) D. J. Mack and J. T. Njardarson, ACS Catal., 2013, 3, 272; (e) D.-H. Zhang, X.-Y. Tang and M. Shi, Adv. Chem. Res., 2014, 47, 913; (f) M. A. Cavitt, L. H. Phun and S. France, Chem. Soc. Rev., 2014, 43, 804; (g) T. F. Schneider, J. Kaschel and D. B. Werz, Angew. Chem., Int. Ed., 2014, 53, 5504; (h) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, Chem. Rev., 2014, 114, 7317; (i) I. Marek, A. Masarwa, P.-O. Delaye and M. Leibeling,
For reviews for cyclobutanes, see: ref. 2.

For selected examples for selective proximal bond cleavage reactions, see: (a) T. Ichiyanagi, S. Kuniyama, M. Shimizu and T. Fujiwasa, Chem. Lett., 1997, 26, 1149; (b) Y. Koga and K. Narasaka, Chem. Lett., 1999, 28, 705; (c) S. C. Bart and P. J. Chirik, J. Am. Chem. Soc., 2003, 125, 886; (d) L. Liu and J. Montgomery, J. Am. Chem. Soc., 2006, 128, 5348; (e) S. Ogoshi, M. Nagata and H. Kurosawa, J. Am. Chem. Soc., 2006, 128, 5350; (f) L. Liu and J. Montgomery, Org. Lett., 2007, 9, 3885; (g) T. Tamaki, M. Nagata, M. Ohashi and S. Ogoshi, Chem.-Eur. J., 2009, 15, 10083; (h) A. B. Chaplin and A. S. Weller, Organometallics, 2010, 29, 2332; (i) T. Tamaki, M. Ohashi and S. Ogoshi, Angew. Chem., Int. Ed., 2011, 50, 12067; (j) M. H. Shaw, E. Y. Melikhova, D. P. Kloer, W. G. Whittingham and J. F. Bower, J. Am. Chem. Soc., 2013, 135, 4992; (k) M. H. Shaw, N. G. McClearan, W. G. Whittingham and J. F. Bower, J. Am. Chem. Soc., 2015, 137, 463; (l) M. H. Shaw, R. A. Croft, W. G. Whittingham and J. F. Bower, J. Am. Chem. Soc., 2015, 137, 8054; (m) G.-W. Wang, N. G. McClearan, M. H. Shaw, W. G. Whittingham and J. F. Bower, J. Am. Chem. Soc., 2016, 138, 13501; (n) M. H. Shaw, W. G. Whittingham and J. F. Bower, Tetrahedron Lett., 2016, 57, 2731; (o) R. Ye, B. Yuan, J. Zhao, W. T.Ralston, C.-Y. Wu, E. U. Barin, F. D. Toste and G. A. Somorjai, J. Am. Chem. Soc., 2016, 138, 8533; For selected examples for selective distal bond cleavage reactions: (p) M. Murakami, H. Ami, K. Shigeto and Y. Ito, J. Am. Chem. Soc., 1996, 118, 8285; (g) Z. He and A. K. Yudin, Org. Lett., 2006, 8, 5829.

For reviews, see: (a) O. Riant, N. Mostefai and J. Courmarcel, Synthesis, 2004, 2943; (b) B. Marcinec, Coord. Chem. Rev., 2005, 249, 2374; (c) S. Diez-González and S. P. Nolan, Acc. Chem. Res., 2008, 41, 349; (d) K. Riener, M. P. Högerl, P. Gigler and F. E. Kühn, ACS Catal., 2012, 2, 613; (e) Y. Nakajima and S. Shimada, RSC Adv., 2015, 5, 20603.

For recent examples for the synthesis of α-aminosilanes: (a) N. Niljianskul, S. Zhu and S. L. Buchwald, Angew. Chem., Int. Ed., 2015, 54, 1638; (b) K. Kato, K. Hirano and M. Miura, Angew. Chem., Int. Ed., 2016, 55, 14400 and references therein.

1 Another ring-opened product was obtained, see the ESI.†

12 N-Prooplypivalamides, which was generated via C–C bond cleavage and hydrogenation, was formed, see the ESI.†

10 For details regarding the regioselectivities of each product, see the ESI.†

14 The main byproducts were desilylated products in 10–30% yield. When tert-butyl acrylate was added as a hydrogen scavenger, these byproducts were suppressed to less than 10% yield. However, in such cases, the product yields did not increase, as the amount of recovered starting material 1 increased.

15 K. Tamao, N. Ishida, T. Tanaka and M. Kumada, Organometallics, 1983, 2, 1694.

16 Examples of Rh-catalyzed hydrosilylation of enamides: (a) T. Murai, T. Oda, F. Kimura, H. Onishi, T. Kanda and S. Kato, J. Chem. Soc., Chem. Commun., 1994, 2143; (b) G. W. Hewitt, J. J. Somers and S. M. Sieburth, Tetrahedron Lett., 2000, 41, 10175; (c) G. K. Min and T. Skrydstrup, J. Org. Chem., 2012, 77, 5894.

17 An example of Rh-catalyzed hydrosilylation of allylamine: A. J. Huckaba, T. K. Hollis and S. W. Reilly, Organometallics, 2013, 32, 6248.

18 S. Sakaki, M. Sumimoto, M. Fukushima, H. Fujimoto and S. Matsuzaki, Organometallics, 2002, 21, 3788.

19 See the ESI.†

20 (a) C. A. Tolman, Chem. Rev., 1977, 77, 313. For the cone angle of P(1-nap): (b) H. Bahrmann and B. Fell, J. Mol. Catal., 1980, 8, 329.