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New cyclization reactions in organic syntheses*

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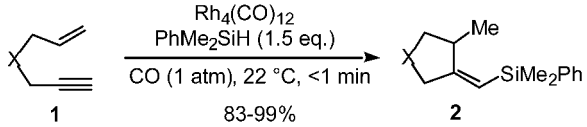
Abstract: Recent development in the transition metal-catalyzed cyclization reactions for organic syntheses in the author's laboratories is summarized, which includes (i) novel silylcarbocyclizations (SiCaCs) and carbonylative carbotricyclizations, (ii) intramolecular silylformylations and desymmerization of siloxydiynes by sequential double silylformylation, (iii) efficient total synthesis of (+)-prosopinine, (iv) enantioselective desymmetrization of aminodienes, and (iv) new and efficient routes to 1-azabicyclo[x.y.0]alkane amino acids. All these processes are catalyzed by Rh or Rh–Co complexes, and useful for rapid and efficient construction of a variety of heterocyclic and carbocyclic compounds. Mechanisms of these new carbocyclization and cyclohydrocarbonylation reactions are also discussed.

It has been the central focus in modern organic synthesis to develop highly efficient catalytic processes for the syntheses of natural and unnatural compounds of medicinal interest or intermediates useful for functional materials. One of the most attractive approaches to such aims is to apply transition metal-catalyzed cyclization reactions for the transformations of simple starting materials into monocyclic, bicyclic, and polycyclic scaffolds that can be further elaborated into specific targets.

This account describes new and useful cyclization processes based on silylcarbocyclization (SiCaC), silylformylation, and cyclohydrocarbonylation reactions, which have recently been developed in these laboratories and will find many applications in organic syntheses.

SILYLCARBOCYCLIZATIONS (SiCaCs)

The first silylcarbocyclization was discovered serendipitously during our detailed product analysis of the silylformylation of 1-hexyne catalyzed by Rh and Rh–Co carbonyl clusters, which gave dibutylcyclopentenone by incorporating two molecules of 1-hexyne, one molecule of hydrosilane, and one molecule of CO. Following up this discovery, we have investigated the intramolecular version of this reaction using a variety of 1,6-enynes, which led to the discovery of novel silylcarbocyclization (SiCaC) reaction (eq. 1) [1–3]. The SiCaC reaction of 1,6-enynes is catalyzed by $Rh_4(CO)_{12}$ and $Rh_2Co_2(CO)_{12}$,



X = $C(CO_2R)_2$, $C(CH_2OR)_2$, N-Ts, N-R, O, etc. (1)

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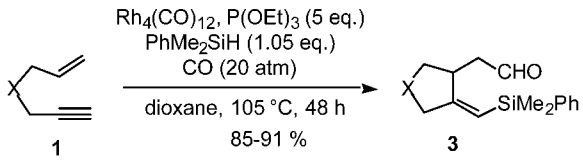
which enable the reaction to proceed at ambient temperature and completes mostly within a minute. Other Rh catalysts such as $Rh(acac)(CO)_2$ are also effective for this reaction, but require 65–70 °C to promote the reaction efficiently. Although CO is not incorporated into the SiCaC products, the cluster catalysts require CO atmosphere to stabilize the active catalyst species [1–3].

When the SiCaC reaction of an enyne with a hydrosilane is carried out under higher pressure of CO (20 atm) at dilute conditions and/or in the presence of a phosphite ligand (5 equiv/Rh), carbonylative SiCaC reaction (CO–SiCaC) takes place virtually exclusively (eq. 2) [3].

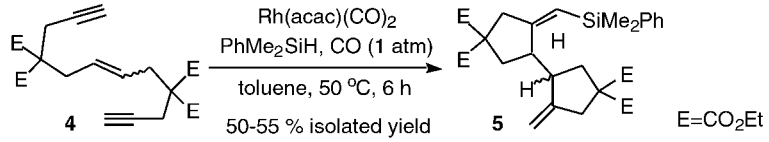


(2)

The SiCaC reaction is applicable to 5-alkynals, which afford 2-exo-silylmethylenecyclopentanols in high yields [4]. The SiCaC reactions that accompany subsequent hydrosilylation (SiCaC–HS) have also been studied [2]. We have also discovered and developed novel Rh-catalyzed silylcarbobicyclization (SiCaB) of 1,6-diynes, which gives the corresponding 2-silylbicyclo[3.3.0]oct-$\Delta^{1,5}$-en-3-ones [5] or 2-silylbicyclo[3.3.0]octa-1,5-dien-3-ones [6], depending on the specific reaction conditions, in excellent yields.

CASCADE SILYLCARBOCYCLIZATIONS

Mechanistic analysis of SiCaC reactions indicates that cascade silylcarbocyclization reactions are possible through successive intramolecular carbocyclizations as long as competing reductive elimination is slower than carbometalation. For example, the reaction of dodec-6-ene-1,11-diyne **4** with $PhMe_2SiH$ catalyzed by $Rh(acac)(CO)_2$ at 50 °C and atmospheric pressure of CO gives bis(*exo*-methylenecyclopentyl) **5** (eq. 3) [7]. The reaction is stereospecific, i.e., (6*E*)- and (6*Z*)-dodec-6-ene-1,11-diynes, (*E*)-**4** and (*Z*)-**4**, afford (*R**,*R**)-**5** and (*S**,*R**)-**5**, respectively.

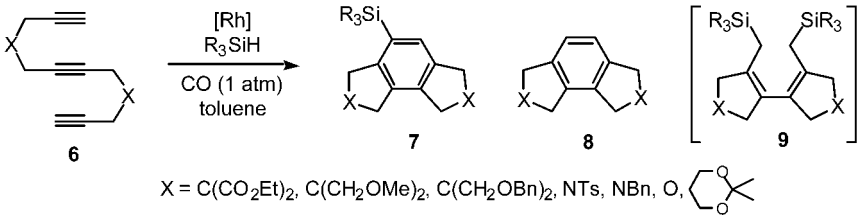


(3)

Although there was a possibility that the third carbocyclization takes place to form a tricyclic product, this process did not occur. This was attributed to the rotational freedom of the C–C bond connecting two cyclopentyl moieties in a key intermediate, i.e., the carbocyclization process cannot compete with reductive elimination.

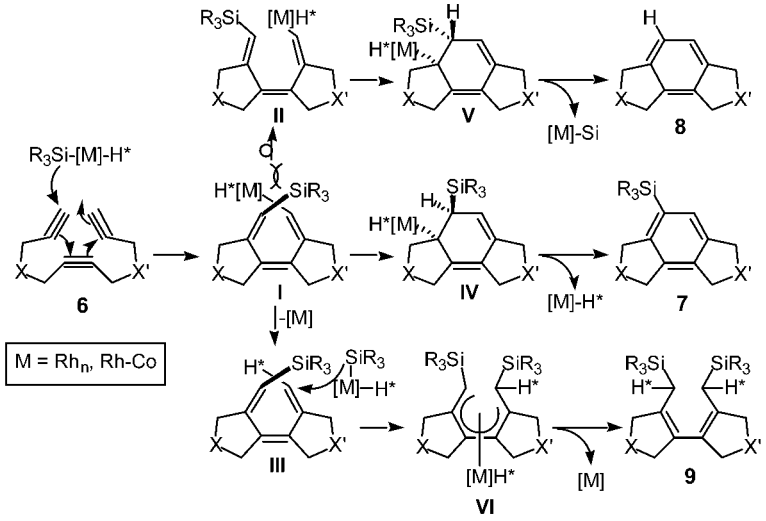
It was anticipated, therefore, that restricting the rotational freedom of the C–C bond connecting two cyclopentyl moieties by incorporating a double bond would make the third carbocyclization possible [8]. Indeed, the reaction of dodeca-1,6,11-triyne **6** [X = $C(CO_2Et)_2$] under the standard SiCaC conditions using $Rh(acac)(CO)_2$ as the catalyst and $PhMe_2SiH$ as the hydrosilane at 70 °C gave a 2:2:1 mixture of **7**, **8**, and **9** in 94% total yield, achieving the first silylcarbotricyclization (SiCaT) via three consecutive carbocyclizations (Scheme 1) [8]. Under optimized conditions using $Rh_4(CO)_{12}$ as the catalyst and 2 equiv of hydrosilane to **6** at 22 °C, fused tricyclic silylbenzene **7** was obtained in excellent yield with 84–93% selectivity. Several Rh complexes were found to be effective in the SiCaT reaction, which are $Rh(acac)(CO)_2$, $[Rh(NBD)_2Cl]_2$, $[Rh(COD)_2Cl]_2$, $Rh_4(CO)_{12}$, and $Rh_2Co_2(CO)_{12}$. A variety of hydrosilanes such as $PhMe_2SiH$, Ph_2MeSiH, Ph_3SiH, Et_3SiH, *t*-$BuMe_2SiH$, $(EtO)_3SiH$, and $(EtO)_2MeSiH$, can be used in this reaction. Various 1,6,11-triynes including those with oxygen and/or

nitrogen atoms in the backbone are proven to be good substrates for this process. Fused tricyclic benzene **8** was formed exclusively using exactly stoichiometric amount of $PhMe_2SiH$.



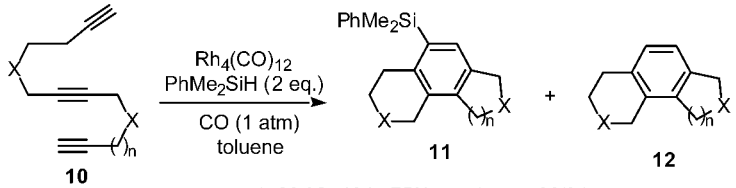
Scheme 1

A proposed mechanism for the SiCaT reaction is illustrated in Scheme 2, which includes initial insertion of an alkyne moiety of **6** into the Si-[Rh] bond of the active catalyst species followed by three consecutive carbometallations [8]. Deuterium labeling experiment confirmed the cascade process and eliminated the involvement of any common metallacycle in the catalytic cycle. The formation of the non-silyl product **8** is explained by the occurrence of the Ojima–Crabtree-type rearrangement [9] of intermediate **I** and β-silyl elimination of Si-[M] species from intermediate **V** [8].



Scheme 2

The SiCaT reaction is applicable to the construction of 6-6-5 and 6-6-6 fused tricyclic skeletons such as **11** and **12** (eq. 4) [8]. Since the formation of 6-membered ring other than benzene ring by catalytic carbocyclization is demanding in general, the ability to construct such ring systems is synthetically significant and advantageous. Also, the 6-6-5 and 6-6-6 fused ring systems find plenty of applications to the syntheses of medicinally active compounds.

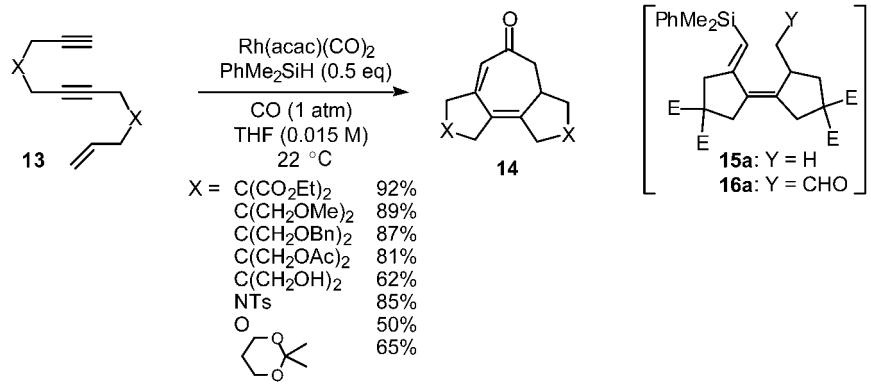


a: n = 1, 22 °C, 40 h, 75%, **11a**/**12a** = 66/34
b: n = 2, 40 °C, 24 h, 69%, **11b**/**12b** = 48/52

(4)

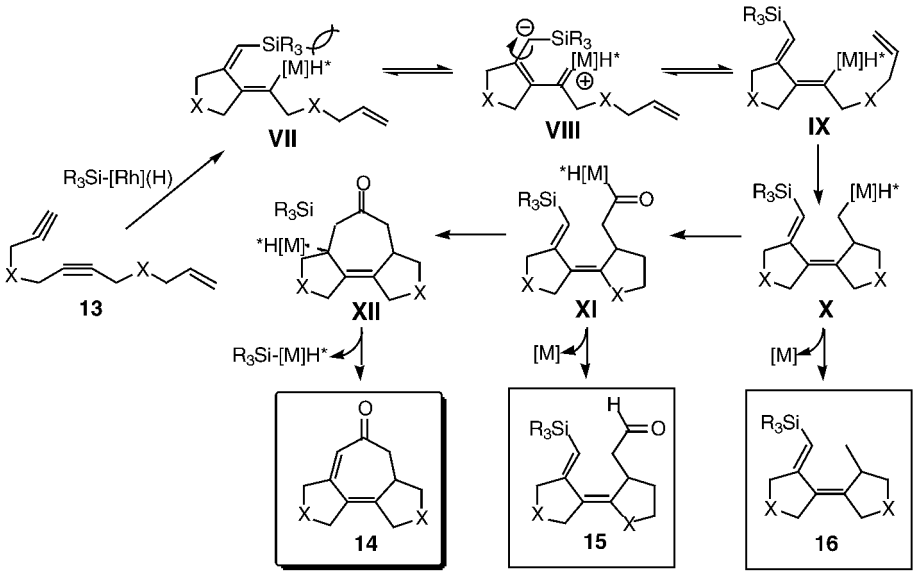
CARBONYLATIVE CARBOTRICYCLIZATION OF ENEDIYNES

As an extension of the SiCaT reaction, the reaction of dedec-11-ene-1,6-diyne **13a** [X = $C(CO_2Et_2)_2$] with $PhMe_2SiH$ catalyzed by $Rh(acac)(CO)_2$ was carried out at 70 °C and CO atmosphere with expectation of obtaining 5-6-5 tricyclic product. However, the reaction gave cyclopenta[e]azulene **14a** and bis(cyclopentylidene) **15a** as major products and aldehyde **16a** as minor product in 70% overall yield (**14a**:**15a**:**16a** = 36:43:21) (Scheme 3) [10]. This marks the serendipitous discovery of the novel and synthetically very attractive carbonylative carbotricyclization process incorporating CO, forming 5-7-5 fused ring system.



Scheme 3

Although silyl group is not included in **14a**, no reaction takes place after 72 h in the absence of a hydrosilane, recovering the starting enediyne **13a**. Thus, hydrosilane is proven necessary for this reaction to occur. A possible mechanism that can accommodate the formations of **14**, **15**, and **16** is shown in Scheme 4 [10].

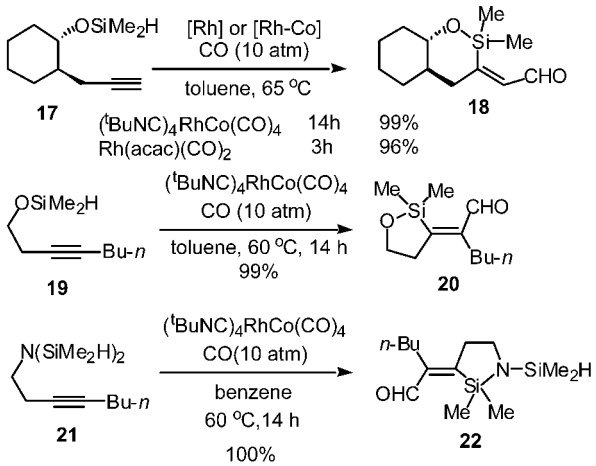


Scheme 4

It is clear from this mechanism that only a catalytic amount of a hydrosilane should be necessary for the formation of **14** since the catalytically active Si-[Rh] species should be regenerated from intermediate **XII** [10]. In fact, the use of a catalytic amount of $PhMe_2SiH$ brought about the exclusive formation of **14** by totally shutting out the formations of **15** and **16**. Under the optimized conditions, i.e., the use of 0.5 equiv of $PhMe_2SiH$ at high dilution (0.015 M) in THF, **14a** was obtained in 92% isolated yield as the sole product (Scheme 3). Various functional groups, e.g., ether, ester, hydroxyl, and sulfonamide, and heteroatoms in the backbone of enediynes **14** are well tolerated in this reaction to give the corresponding fused 5-7-5 tricyclic products **15** in good to excellent isolated yields [10]. Other rhodium catalysts, $Rh(acac)(CO)_2$, $Rh_4(CO)_{12}$, and $[Rh(CO)_2Cl]_2$, show similar efficacy. As hydrosilane, $PhMe_2SiH$ is the best, but Ph_2MeSiH, $(EtO)_3SiH$, and Et_3SiH can also be used.

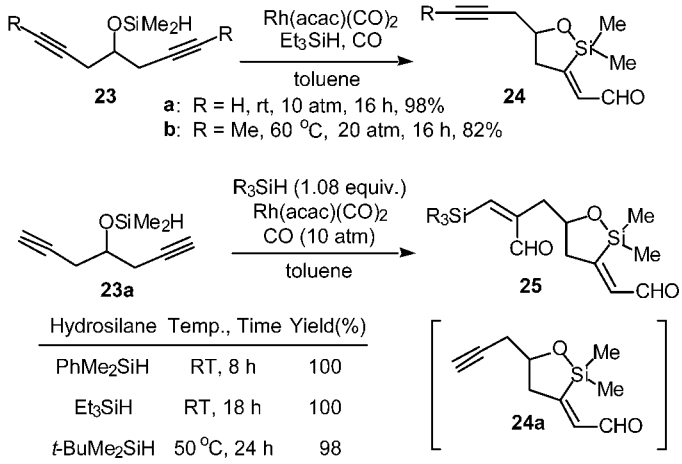
DESYMMETRIZATION OF HYDROSILOXYALKADIYNES BY INTRAMOLECULAR SILYLFORMYLATION

Silylformylation of 1-alkynes has been extensively studied, which gives (*Z*)-1-silyl-2-formyl-1-alkenes with complete regio- and stereoselectivity [11]. The reaction of internal alkynes, however, is not regioselective. Accordingly, the intramolecular directed silylformylation has been developed to obtain the products with opposite regiochemistry as well as to achieve complete regio-control. For example, the reactions of ω-dimethylsiloxyalkynes **17** and **19** catalyzed by Rh and Rh–Co complexes proceed via *exo-dig* cyclization to give the corresponding 5-*exo*-formylalkylideneoxasilacycloalkanes **18** and **20**, respectively, in excellent yields (Scheme 5) [12]. This reaction is applicable to *ω*-disilylaminoalkynes, which gives aza-1-silacyclopentanes, e.g., **21** → **22** [13].



Scheme 5

Intramolecular silylformylation has successfully been applied to the desymmetrization of dimethylsilyloxyalkadiynes **23** catalyzed by $Rh(acac)(CO)_2$, which affords 5-*exo*-(formylmethylene)oxasilacyclopentanes **24** in high yields (Scheme 6) [14]. Novel sequential double silylformylation of **23a** also affords desymmetrization products 3-(3-silyl-2-formylprop-2-enyl)-5-*exo*-(formylmethylene)oxasilacyclopentanes **25** in excellent yields. It has been shown that the intramolecular silylformylation is much faster than the intermolecular reaction so that **24a** is formed exclusively in the beginning, followed by the second and intermolecular reaction to give **25** cleanly just by mixing all reactants at once (Scheme 6) [14]. These products are useful intermediates for the syntheses of polyhydroxy compounds of biological interest.

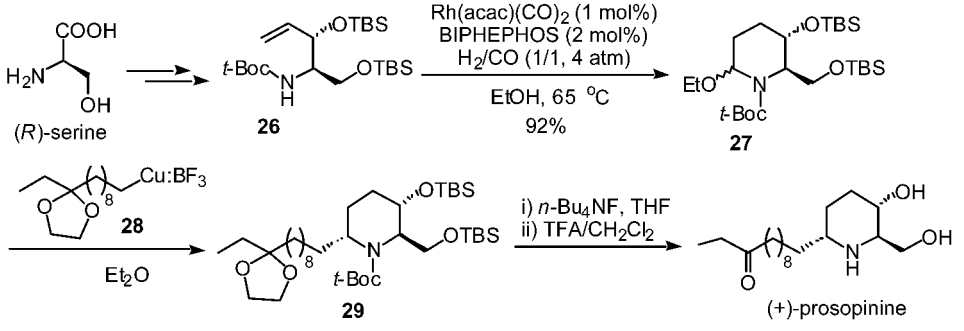


Scheme 6

TOTAL SYNTHESIS OF ENANTIOPURE (+)-PROSOPININE USING CYCLOHYDROCARBONYLATION IN THE KEY STEP

Cyclohydrocarbonylation reaction of alkenamides, alkenamines, or alkenols catalyzed by transition metals proceeds via hydroformylation followed by condensation of the resulting aldehyde with amide, amine, or alcohol moiety. This reaction provides efficient routes to various nitrogen and oxygen heterocycles.

This reaction has been successfully applied to the syntheses of (+)-prosopinine and (–)-deoxoprosophylline, which provide the shortest routes to these alkaloids in enantiopure form so far reported to date [15]. These piperidine alkaloids exhibit antibiotic and anesthetic properties. The short total synthesis of (+)-prosopinine is shown in Scheme 7 [15].

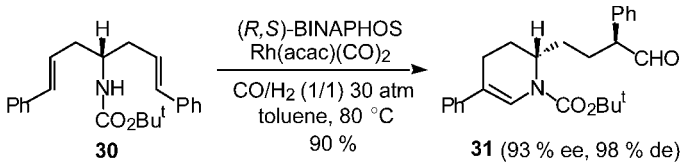


Scheme 7

The synthesis of (+)-prosopinine began with the elaboration of (*R*)-serine, to a *N*-*t*-Boc-homoallylamine **26**, which was subjected to cyclohydrocarbonylation catalyzed by $Rh(acac)(CO)_2$-BIPHEPHOS complex to give the key intermediate 5,6-*trans*-2-ethoxypiperidine **27** in 92% yield. Ethoxypiperidine **27** was converted to (+)-prosopinine through the nucleophilic displacement of the ethoxy group with organocopper reagent **28**, followed by deprotections via **29**.

ENANTIOSELECTIVE DESYMMETRIZATION OF AMINODIENES

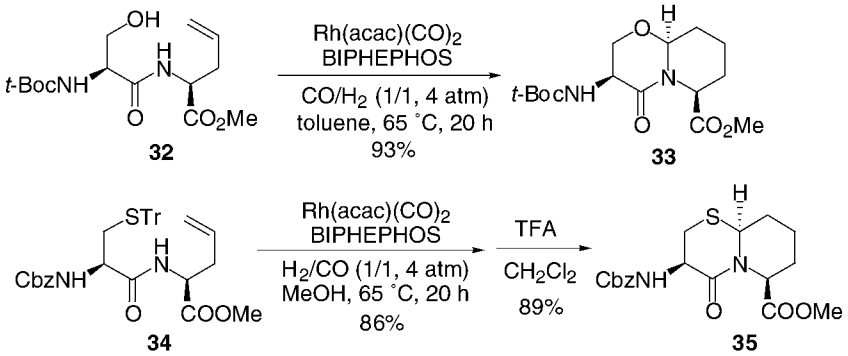
Enantioselective cyclohydrocarbonylation has recently been applied to the efficient desymmetrization of 4-amido-1,6-dienes. For example, the reaction of 4-*t*-Boc-amino-1,7-diphenyl-1,6-heptadiene (**30**) catalyzed by Rh(acac)$(CO)_2$-(*R,S*)-BINAPHOS) in toluene at 60 °C and 30 atm of CO and H_2 (1:1) gave 1-*t*-Boc-5,6-didehydropiperidine **31** with 93% ee and 98% de in 90% yield (eq. 5).[16] This type of enantio- and diastereoselective desymmetrization will find many applications in organic syntheses. Further studies on the scope of this reaction is actively underway in these laboratories.



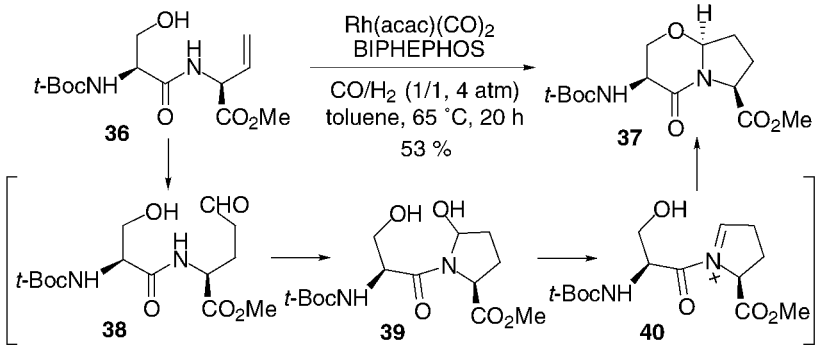
(5)

NEW AND EFFICIENT ROUTES TO 1-AZABICYCLO[X.Y.0]ALKANE AMINO ACIDS

Azabicyclo[x.y.0]alkane amino acids serve as conformationally restricted dipeptide surrogates, which are increasing their importance in the design of peptides and peptidomimetics for enzyme inhibitors and receptor antagonists or agonists. The cyclohydrocarbonylation has been successfully employed for the rapid syntheses of a variety of 1-azabicyclo[x.y.0] alkane amino acids directly from dipeptide substrates. Three examples are shown in Schemes 8 and 9 [17].



Scheme 8



Scheme 9

Reaction of (*S,S*)-*N*-*t*-boc-cysteylvinylglycinate **36** under the standard cyclohydrocarbonylation conditions gave the corresponding 5-oxa-1-azabicyclo[4.3.0]nonane amino acid ester **37**. This reaction includes Rh-BIPHEPHOS catalyzed extremely linear selective hydroformylation to form aldehyde **38**, followed by the formation of hemiamidal **39**, subsequent generation of acyliminium ion **40**, and the intramolecular nucleophilic addition of the hydroxyl group of the serine moiety to **40** to yield **37** (Scheme 9) [17].

CONCLUSION

Recent advances in the development of new cyclization reactions catalyzed by Rh complexes in these laboratories are summarized. These new reactions provide powerful methods for the rapid construction of a variety of skeletons relevant to biological active natural and unnatural substances. Cascade carbocyclizations will find many applications in the syntheses of fused carbocyclic and heterocyclic compounds and will be applicable to library syntheses.

ACKNOWLEDGMENTS

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REFERENCES

1. I. Ojima, R. J. Donovan, W. R. Shay. *J. Am. Chem. Soc*. **114**, 6580 (1992).
2. I. Ojima, J. W. Zhu, E. S. Vidal, D. F. Kass. *J. Am. Chem. Soc*. **120**, 6690 (1998).
3. S. Y. Lee. Ph.D. Thesis, State University of New York at Stony Brook (2000).
4. I. Ojima, M. Tzamarioudaki, C.-Y. Tsai. *J. Am. Chem. Soc.* **116**, 3643 (1994).
5. I. Ojima, D. A. Fracchiolla, R. J. Donovan, P. Banerji. *J. Org. Chem*. **59**, 7594 (1994).
6. I. Ojima, D. F. Kass, J.-W. Zhu. *Organometallics* **15**, 5191 (1996).
7. I. Ojima, J. V. McCullagh, W. R. Shay. *J. Organomet. Chem.* **521**, 421 (1996).
8. I. Ojima, A. T. Vu, J. V. McCullagh, A. Kinoshita. *J. Am. Chem. Soc*. **121**, 3230 (1999).
9. (a) I. Ojima, N. Clos, R. L. Donovan, P. Ingallina. *Organometallics* **9**, 3127 (1990); (b) R. S. Tanke and R. H. Crabtree. *J. Am. Chem. Soc*. **112**, 7984 (1990).
10. I. Ojima and S. Y. Lee. *J. Am. Chem. Soc*. **122**, 2385 (2000).
11. For a comprehensive review, see I. Ojima, C.-Y. Tsai, M. Tzamarioudaki, D. Bonafoux. In *Organic Reactions*, L. E. Overman (Ed.), Vol. 56, pp. 1–354, Wiley, New York (2000).
12. I. Ojima, E. S. Vidal, M. Tzamarioudaki, I. Matsuda. *J. Am. Chem. Soc.* **117**, 6797 (1995).
13. I. Ojima and E. S. Vidal. *Organometallics* **18**, 5103 (1999).
14. D. Bonafoux and I. Ojima. *Org. Lett.* 1303–1305 (2001).
15. I. Ojima and E. S. Vidal. *J. Org. Chem*. **63**, 7999 (1998).
16. Z. Hua, N. Mizutani, P. Y. Zhang, I. Ojima. *221st American Chemical Society National Meeting, Abstracts* ORGN394 (2001).
17. N. Mizutani and I. Ojima. *221st American Chemical Society National Meeting, Abstracts*, ORGN395 (2001).