

# SYNFORM

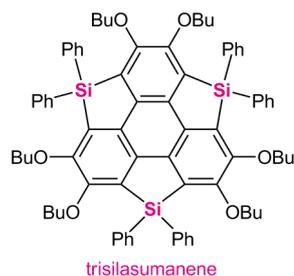
People, Trends and Views in Synthetic Organic Chemistry

2010/01

## SYNSTORIES ■ ■ ■ ■

■ **Asymmetric Synthesis of  $\beta$ -Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation**

■ **Development of a Sila-Friedel-Crafts Reaction and Its Application to the Synthesis of Dibenzosilole Derivatives**



■ **Formal [4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans**

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**Dear readers,**

This new issue of **SYNFORM** is the first of 2010, and I hope you will agree that the three **SYNSTORIES** featured in this inaugural issue are a very good way to begin the fourth year of life of **SYNFORM**. Tamio Hayashi

and his group (Japan) are protagonists of the first **SYNSTORY** of the year, which is about the enantioselective rhodium-catalyzed conjugate alkylation of  $\alpha,\beta$ -unsaturated aldehydes recently developed in Hayashi's lab. Jeffrey Johnson (USA) in the second **SYNSTORY** tells us more about his recent stereoselective method to synthesize substituted tetrahydropyrans. Takayuki Kawashima, in the third **SYNSTORY**, describes the fascinating synthesis of dibenzosilole derivatives through a Sila-Friedel–Crafts reaction. Three pieces of research carrying the hallmark of quality!

Enjoy your reading!

**Matteo Zanda**

*Editor of SYNFORM*

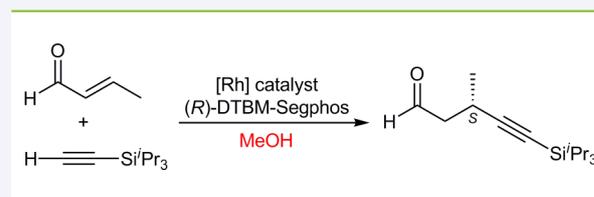
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[Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

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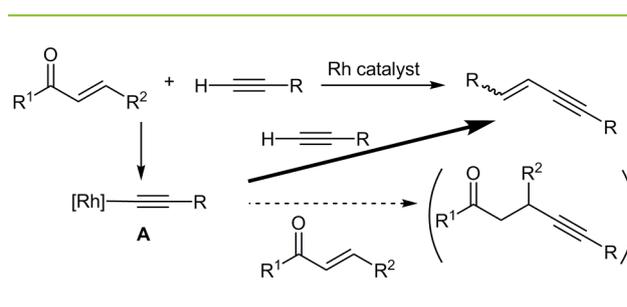
## Asymmetric Synthesis of $\beta$ -Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation

*Angew. Chem. Int. Ed.* **2009**, *48*, 8057–8059

■ Catalytic asymmetric conjugate addition of terminal alkynes to  $\alpha,\beta$ -unsaturated carbonyl compounds provides a powerful method to construct a stereogenic carbon center at the propargylic position with a high atom efficiency. In 2008, the group of Professor Tamio Hayashi from the Department of Chemistry, Kyoto University (Japan), reported the asymmetric conjugate addition of (triisopropylsilyl)acetylene to  $\alpha,\beta$ -unsaturated ketones catalyzed by a rhodium complex coordinated to a bulky bisphosphine ligand, DTBM-Segphos. The reaction gave high yields of chiral  $\beta$ -alkynyl ketones (*J. Am. Chem. Soc.* **2008**, *130*, 1576), thanks to the effective suppression of the dimerization of (triisopropylsilyl)acetylene.

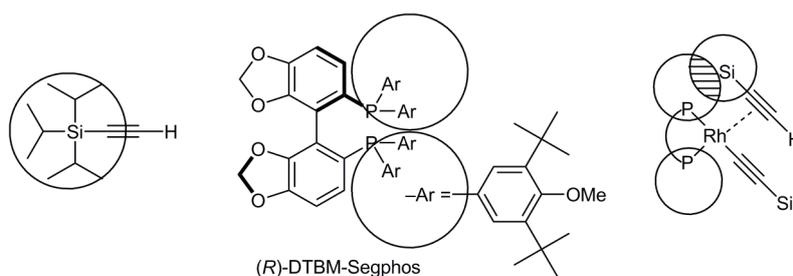


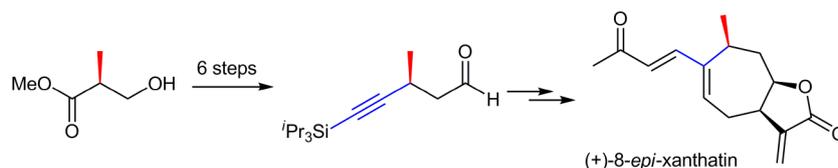
Indeed, the reaction of less bulky silylacetylenes in the presence of a less bulky phosphine ligand usually gave the alkyne dimers as major products.



Recently, Professors Hayashi and Nishimura were able to extend the methodology to  $\beta$ -alkynyl aldehydes. This achievement is very important because the  $\beta$ -alkynyl aldehydes produced by this reaction are important chiral building blocks in organic synthesis. “A typical example of the importance of  $\beta$ -alkynyl aldehydes is the synthesis of (+)-8-*epi*-xanthatin reported by Professor Stephen F. Martin from the University of Texas at Austin (USA), where the key chiral  $\beta$ -alkynyl aldehyde, (*S*)-3-methyl-5-(triisopropylsilyl)pent-4-ynal, was derived from enantiopure methyl 3-hydroxy-2-methylpropanoate in six steps,” explained Professor Nishimura.

“It looks very easy and straightforward to apply the asymmetric conjugate alkynylation protocol to the synthesis of  $\beta$ -alkynyl aldehydes, but in reality it is not that simple,” continued Professor Nishimura. “In fact, the reaction of but-2-





enal with (triisopropylsilyl)acetylene under the same reaction conditions as used for  $\alpha,\beta$ -unsaturated ketones gave 1,3-bis(alkynyl)butanol as a major product.” Professors Hayashi and Nishimura found that changing the solvent from 1,4-dioxane to methanol dramatically improved the selectivity affording the  $\beta$ -alkynyl aldehydes exclusively, without any other side products. “The high efficiency of using methanol as a solvent has been previously reported by Miyaura (*J. Org. Chem.* **2000**, *65*, 4450) for the conjugate addition of arylboronic acids to enals,” explained Professor Nishimura.



“The  $\beta$ -alkynyl aldehydes obtained here are highly useful as chiral building blocks for the synthesis of natural products,” said Professor Nishimura. “Deprotection of the silyl group from the alkyne terminus or the modification of the aldehyde functionality is readily performed without loss of enantiomeric purity.”

“The rhodium-catalyzed asymmetric conjugate alkylation still faces major problems like limitation of the substrate scope, low efficiency of the catalyst, and so on. We are approaching the problems to make the asymmetric conjugate alkylation more general and more practically useful,” concluded Professor Hayashi.

### About the authors

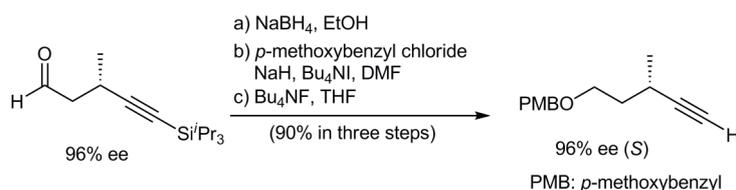


Prof. T. Hayashi

**Tamio Hayashi** graduated from Kyoto University (Japan) in 1970. He received his PhD in 1975 from Kyoto University under the direction of Professor Makoto Kumada. The title of his thesis was “Catalytic Asymmetric Hydrosilylation of Olefins and Ketones”. Then, he was appointed as a Research Associate at the Faculty of Engineering, Kyoto University. He spent the year 1976 to 1977 as a Postdoctoral Fellow at Colorado State University (USA) with Professor Louis S. Hegedus. He was promoted to Full Professor in 1989 in the Catalysis Research Center, Hokkaido University (Japan). Since 1994, he has been a Full Professor at the Faculty of Science, Kyoto University. His awards include the Award for Young Chemists of the Society of Synthetic Organic Chemistry (Japan) in 1983, the IBM Japan Prize in 1991, The Chemical Society of Japan Award in 2003, the Thomson Scientific Research Front Award in 2004, the Molecular Chirality Award in 2005, The Ryoji Noyori Prize and the Author C. Cope Scholar Award in 2008. Tamio Hayashi has published more than 300 original papers with a total citation number of around 21000 (*h*-index 80) by October 2009. He has been interested in the development of new reactions catalyzed by transition-metal complexes, especially in catalytic asymmetric reactions.

>>

### Matteo Zanda





*Prof. T. Nishimura*

**Takahiro Nishimura** was born in Kumamoto (Japan) in 1970. He received his BSc in 1994 and PhD in 2001 from Kyoto University under the supervision of Professor Sakae Uemura. He became an Assistant Professor at Graduate School of Engineering, Kyoto University in 2001. From 2004 to 2005, he was a Postdoctoral Fellow at The University of North Carolina (USA) with Professors Maurice Brookhart and Joseph L. Templeton.

In 2005, he was promoted to Lecturer at Graduate School of Science, Kyoto University. He was awarded an Incentive Award in Synthetic Organic Chemistry (Japan) in 2007. His current research interest is the development of new catalytic organic reactions using transition metals.



*Mr. T. Sawano*

**Takahiro Sawano** was born in Shizuoka (Japan) in 1986. He received his BSc degree from Tohoku University (Japan) in 2008 under the supervision of Professor Minoru Ueda. He is currently an MSc course graduate student in the group of Professor Tamio Hayashi. His current research interest is the development of transition-metal-catalyzed organic transformations using terminal alkynes.

# Formal [4+2] Cycloaddition of Donor–Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans

*J. Am. Chem. Soc.* **2009**, *131*, 14202–14203

■ Cycloaddition reactions are very useful tools in an organic chemist's arsenal and have found countless applications in synthesis. Classically, these reactions involve a dipole and a dipolarophile, although several classes of compounds are known to behave as masked dipoles. Among them, appropriately functionalized cyclopropanes are known to be effective substrates in dipolar cycloadditions, whereas the homologous compounds (cyclobutanes) are much less recognized as masked dipoles in spite of their high ring-strain energy. Recently, Professor Jeffrey S. Johnson from the University of North Carolina (USA) described a powerful methodology which makes use of functionalized donor–acceptor cyclobutanes in a formal [4+2] cycloaddition with aldehydes to give substituted tetrahydropyrans.

“We had two motivations in undertaking this project,” explained Professor Johnson. “First, we were simply interested in determining if what we had learned during our studies of cyclopropane/aldehyde annulations would be applicable to a

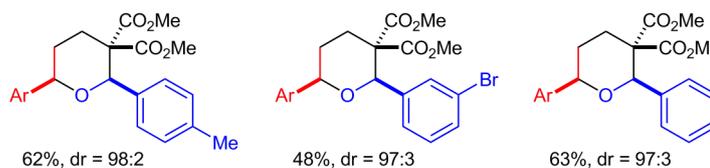
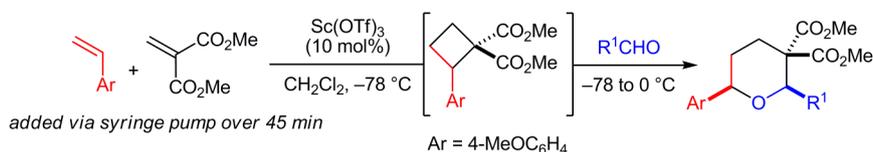
homologous system. At first glance,” continued Professor Johnson, “this would appear to be a relatively trivial modification; however, we were struck by the relative dearth of chemistry associated with donor-acceptor cyclobutanes relative to donor–acceptor cyclopropanes. We believe that this is directly linked to the synthetic availability of the former. No Corey–Chaykovsky reaction exists for cyclobutanes!” According to Professor Johnson, this deficiency prompted the second main question: “Is there a way that we could merge cyclobutane synthesis with the subsequent annulation reaction? Certainly there is no shortage of tetrahydropyran syntheses, but we wished to develop a way where one might ‘snap together’ trivial building blocks in a predictable, advantageous way”, he said.

Prof. Johnson and graduate student Andrew T. Parsons were able to show that these types of annulations are feasible under operationally simple conditions. “Most exciting to us is the discovery that one can make the donor-acceptor cyclo-

## Concept:



## Application:



butane via a catalyzed [2+2] cycloaddition and use the same Lewis acid in the same pot to catalyze the [4+2] annulation,” said Professor Johnson. “The synthesis of arenes and pyridines via [2+2+2] reactions of triple bonds is a well-established reaction, but applying the concept to saturated heterocycles is not a developed concept. We feel this paper provides the experimental blueprint for such annulations,” he concluded. ■

*Matteo Zanda*

### The authors



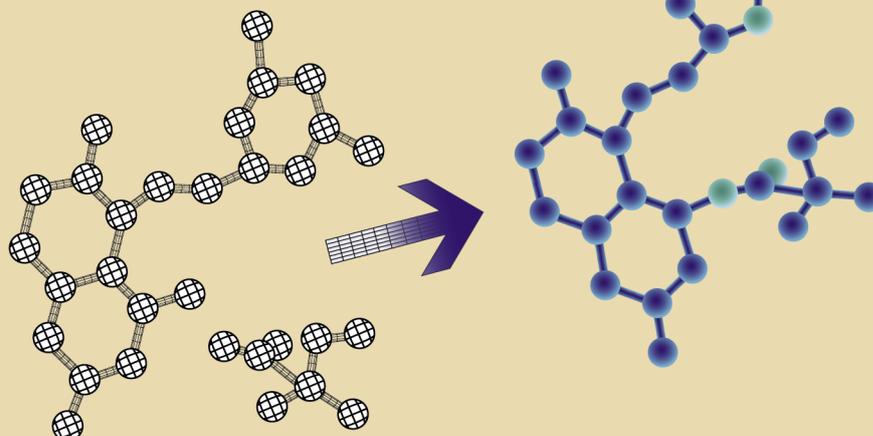
From left: A. T. Parsons, Prof. J. S. Johnson

## INFORMATION ++++

### Synthesis Reviews

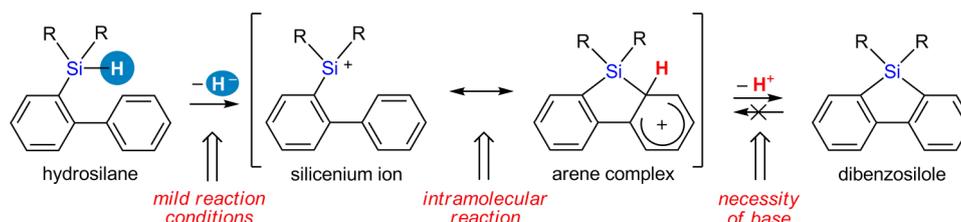
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## Development of a Sila-Friedel–Crafts Reaction and Its Application to the Synthesis of Dibenzosilole Derivatives

*J. Am. Chem. Soc.* **2009**, *131*, 14192–14193

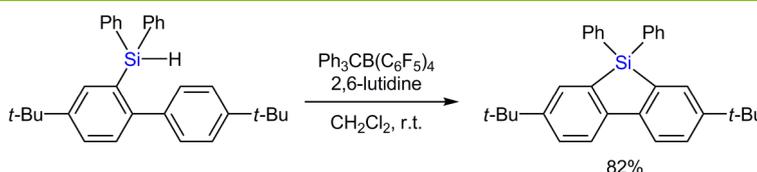


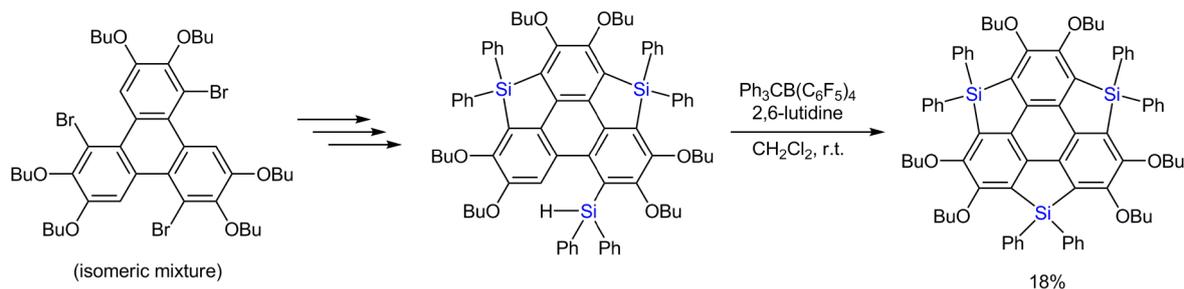
Silole-based  $\pi$ -electron systems are currently receiving much attention as new organic optical materials because of their low-lying LUMOs.  $\pi$ -Extended silole derivatives show desirable properties, such as high fluorescence quantum yields and high glass-transition temperatures. Various synthetic methodologies for the construction of the silole framework have been developed so far. However, these methodologies have been limited to the synthesis of ladder-type or spiro-type compounds. Recently, the group of Professor Takayuki Kawashima and Dr. Junji Kobayashi from the Department of Chemistry, The University of Tokyo (Japan), reported a further step towards the exploration of silole systems; namely, the synthesis of benzosilole derivatives. “We considered that further extension or modification of the silole framework should explore the silole chemistry, because these new molecules would provide improved properties,” said Professor Kawashima. “We focused our attention to the two-dimensionally  $\pi$ -expanded silole derivatives, not to linearly expanded molecules such as ladder-type compounds. However, these compounds are considered to be difficult to synthesize using conventional methods.” Indeed, according to Professor Kawashima, the development of a new type of synthetic methodology will be a keystone for the further progression to two-dimensionally extended derivatives.

As a promising new method, Professor Kawashima and co-workers proposed the direct silylation of an aromatic ring. “The Friedel–Crafts reaction is a well-known method for the direct substitution of an aromatic ring. On the other hand, the sila-Friedel–Crafts reaction – that is, the Friedel–Crafts-type silylation involving a silicenium ion as an intermediate – is known to occur only with electron-rich aromatic rings such as a ferrocene and a pyrrole,” he explained. However, in the case of a non-activated aromatic ring such as benzene, the conversion of the reaction was reported to decrease markedly. “Thus,” continued Professor Kawashima, “the sila-Friedel–Crafts reaction has not been used as a versatile synthetic method to date.” Dr. Kobayashi explained that the difficulties of the sila-Friedel–Crafts reaction can be summarized in three points: 1) difficulty of the generation of silicenium ion, 2) arene– $\text{Si}^+$  complex usually favors  $\pi$ -complex rather than  $\sigma$ -complex, and 3) aryl–Si bonds are easily cleaved by acids.

The basic strategy of the sila-Friedel–Crafts reaction developed by Professor Kawashima and co-workers can be summarized as follows:

- 1) For the generation of a silicenium cation, the authors decided to employ the reaction of a hydrosilane with a trityl cation.
- 2) By using an intramolecular reaction, the reaction should easily proceed due to an entropy effect.





3) The presence of a base is necessary in this reaction to prevent the occurrence of a reverse reaction.

“After the screening of the reaction conditions, the  $\text{Ph}_3\text{CB}(\text{C}_6\text{F}_5)_4/2,6\text{-lutidine}/\text{CH}_2\text{Cl}_2$  system gave the best result,” said Dr. Kobayashi. “Our success in the development of the intramolecular sila-Friedel–Crafts reaction indicated that this reaction might be a new candidate for a synthetic methodology toward the silole skeleton.”

“Indeed,” continued Professor Kawashima, “our methodology can be applied to the synthesis of the ladder-type silole derivative. These results encouraged us to challenge the syn-

thesis of a more difficult target molecule. We tried to apply our method to the synthesis of trisilasumanene, which is a silicon analogue of sumanene, and succeeded in its first synthesis.”

“Now we are going to expand our concept of the intramolecular sila-Friedel–Crafts reaction (electrophilic cyclization) to other main group element analogues such as phosphorus, selenium, and tellurium compounds,” concluded Dr. Kobayashi. ■

*Matteo Zanda*

### About the authors

Shunsuke Furukawa obtained his BSc degree from Hosei University (Japan) and MSc degree from the University of Tokyo. He is currently a PhD course graduate student in Professor Kawashima's group.



Dr. J. Kobayashi

Junji Kobayashi is a Research Associate of the University of Tokyo. He was born in Toyama, Japan in 1973 and received his BSc (1996) and MSc (1998) degrees from the University of Tokyo under the supervision of Professor Renji Okazaki. He became a Research Associate in the research group of Professor Takayuki Kawashima in 2001 and received his PhD from the University of Tokyo in 2001 under his supervision. He was Postdoctoral Researcher at University of Pennsylvania and Iowa State University (USA) from 2003 to 2005. His research interests are focused on organoheteroatom chemistry, especially on the chemistry of fluorescent compounds bearing

main group elements as well as the chemistry of hyper-coordinate compounds with a rigid tetradentate ligand.



Prof. T. Kawashima

Takayuki Kawashima was born in Kanagawa-ken, Japan in 1946 and received his BSc (1969), MSc (1971), and PhD (1974) from the University of Tokyo under the supervision of Professor Naoki Inamoto. He was Research Associate, Lecturer, and Associate Professor in the Department of Chemistry, Faculty of Science, The University of Tokyo from 1974 to 1998 and became a Professor of the Department of Chemistry, Graduate School of Science, The University of Tokyo, in 1998. From 1976 to 1978 he pursued postdoctoral research at Iowa State University and University of Utah (USA). His research interest is centered on organoheteroatom chemistry with an emphasis on the chemistry of small-ring compounds containing a high-coordinate main group element.

COMING SOON ► ► COMING SOON ► ►

## SYNFORM 2010/02 is available from January 22, 2010

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(Focus on an article from the current literature)

■ **Asymmetric Histidine-Catalyzed Cross-Aldol Reactions of Enolizable Aldehydes**  
(Focus on an article from the current literature)

### FURTHER HIGHLIGHTS + + + +

#### SYNTHESIS

**Review on: Catalytic Asymmetric Michael Additions of  $\alpha$ -Cyano Acetates**

(by S. Jautze, R. Peters)

#### SYNLETT

**Account on: Strategies for Heterocyclic Synthesis via Cascade Reactions Based on Ketenimines**

(by P. Lu, Y. Wang)

#### SYNFACTS

**Synfact of the Month in category "Metal-Mediated Synthesis":  
Pd-Catalyzed Conversion of Aryl Triflates to Aryl Fluorides**

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