



Title	Synthesis of Substituted Cyclooctenes through Cross-Coupling Reactions
Author(s)	Murata, Ryuichi; Yoshida, Rakuto; Uraguch, Daisuke et al.
Citation	Synlett, 36(1), 69-74 https://doi.org/10.1055/a-2330-0819
Issue Date	2024-06-03
Doc URL	https://hdl.handle.net/2115/95390
Type	journal article
File Information	Synlett-asano-HUSCUP.pdf



Synthesis of Substituted Cyclooctenes through Cross-Coupling Reactions

Ryuichi Murata^a
 Rakuto Yoshida^b
 Daisuke Uraguchi^{*b,c}
 Keisuke Asano^{*b}

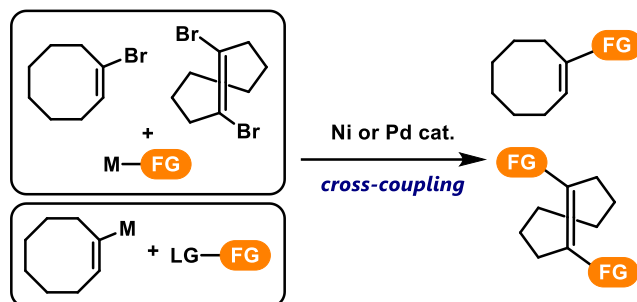
^a Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510, Japan

^b Institute for Catalysis, Hokkaido University, Sapporo, Hokkaido 001-0021, Japan

^c List Sustainable Digital Transformation Catalyst Collaboration Research Platform, Institute for Chemical Reaction Design and Discovery (ICReDD List-PF), Hokkaido University, Sapporo, Hokkaido 001-0021, Japan

uraguchi@cat.hokudai.ac.jp; asano@cat.hokudai.ac.jp

[Click here to insert a dedication.](#)



Received:
 Accepted:
 Published online:
 DOI:

Abstract Cross-coupling methods for the introduction of various substituents into the olefin moiety of cyclooctenes were developed. A range of 1-substituted *cis*-cyclooctenes were synthesized. These protocols unlocked routes to previously inaccessible derivatives, allowing for the syntheses of *cis*-cyclooctenes bearing various functional groups. Moreover, the method was applied to the synthesis of a 1,2-disubstituted *trans*-cyclooctene for the first time, which proved to be a significantly active organocatalyst in relation to the previously developed monosubstituted *trans*-cyclooctene.

Key words substituted cyclooctene, olefin, cross-coupling, expansion of library of functionalized cyclooctenes, organocatalyst

Alkenes are a crucial class of organic compounds,¹ which serve as bioactive agents, photoelectric materials, synthetic intermediates, and ligands for metal catalysts,² among other applications. The unique properties of strained olefins in medium-sized rings, such as cyclooctenes, have garnered significant attention.³ The structural features⁴ and planar chirality^{5,6} of cyclooctenes have been extensively studied. *trans*-Cyclooctenes (TCOs) also demonstrate high reactivity and chemoselectivity toward organic reactions such as inverse electron-demand Diels–Alder reactions, making the olefins valuable in orthogonal bioconjugation reactions.⁷ Furthermore, we investigated additional aspects of olefins by utilizing 1-substituted TCOs as molecular catalysts⁸ and reagents,⁹ in which different olefinic substituents offered a wide range of reaction tools (Figure 1).

Despite the notable utility of cyclooctenes with substituents in the olefin moiety, their synthetic routes remain underdeveloped. Thus, in the process of developing the reaction tools illustrated in Figure 1, we utilized conventional synthetic methods outlined in Scheme 1.¹⁰ While synthetic strategies for structurally diverse organic molecules allow flexibility in designing functional materials, the rigid nature of traditional methods for synthesizing substituted cyclooctenes restricts the range of accessible chemical space. Therefore, it is essential to develop alternative synthetic routes for derivatives that are not accessible through conventional methods. In this context, efficient methods for

synthesizing *cis*-cyclooctenes (CCOs) as well as TCOs are essential to expand the chemistry of medium-sized cyclic olefins.¹¹ However, we encountered three challenges during the synthesis of cyclooctenes. First, the synthesis of CCOs yielded a mixture of regioisomers, **2** and **2'**, which could not be separated owing to their similar properties. This decreased the synthetic efficiency and complicated the assay of pure CCOs. Second, halogen-group-bearing substituents were difficult to synthesize despite their potential to induce electronic and steric effects that influence the functions of cyclooctenes and their roles as synthetic handles for further structural modifications. The complexity arises from the difficulty in preparing the requisite organometallic reagents for introducing substituents (from **1** to **2**) due to the incompatible reactivity of the halogen groups during metalation. Third, there has been no method for synthesizing 1,2-disubstituted TCOs, making it difficult to assess their functions.

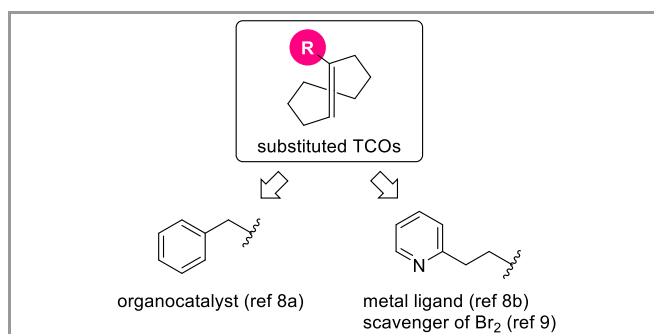
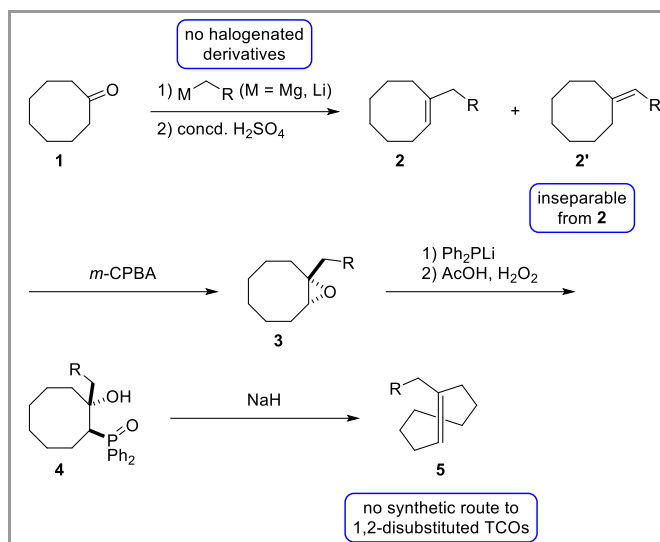
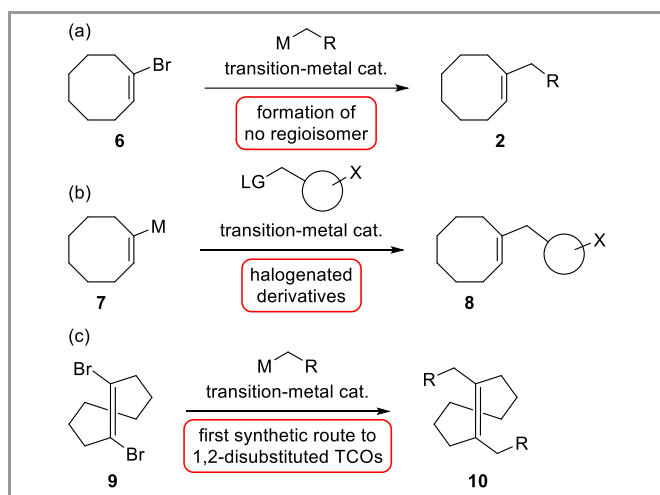


Figure 1 1-Substituted TCOs as reaction tools.



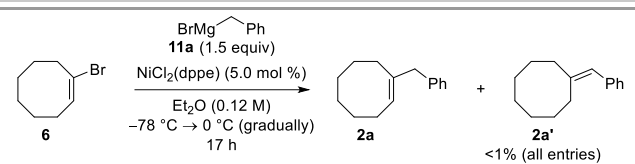
Scheme 1 Conventional methods for synthesizing substituted *cis*- and *trans*-cyclooctenes

To address these challenges, we explored alternative synthetic methods using cross-coupling reactions,¹² because brominated cyclooctenes **6** and **9** can be easily synthesized (Scheme 2). We anticipated several advantages from this approach. First, employing mild conditions allow the selective formation of **2** without yielding regioisomer **2'**, which is crucial for obtaining pure CCOs (Scheme 2a). Second, the cross-coupling of cyclooctenyl metal reagents with halogen-group-bearing electrophiles yields cyclooctenes with halogenated substituents (Scheme 2b). Third, cross-coupling using dibrominated TCO **9** enables the synthesis of 1,2-disubstituted TCOs (Scheme 2c). In this paper, we present the synthetic methods based on cross-coupling reactions that enable the efficient synthesis of a wide range of substituted cyclooctenes.



Scheme 2 Cross-coupling strategies for synthesizing substituted *cis*- and *trans*-cyclooctenes

Table 1 Optimization for Cross-Coupling of **6** and **11a**^a

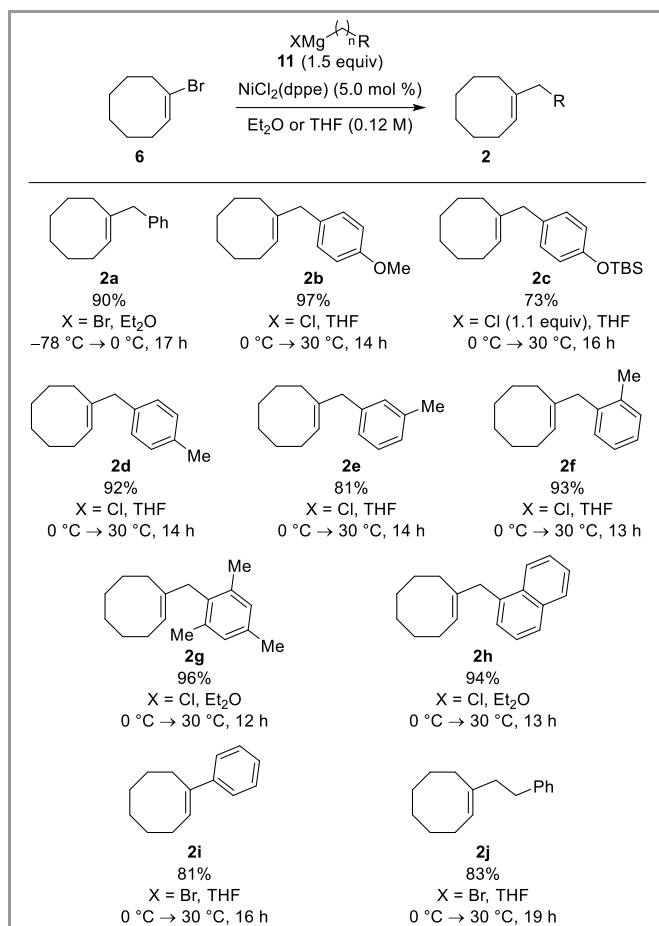


Entry	Deviation from the standard conditions	2a (%) ^b
1	none	98 (90 ^c)
2	NiCl ₂ (PPh ₃) ₂ instead of NiCl ₂ (dppe)	95
3	NiCl ₂ (dppp) ₂ instead of NiCl ₂ (dppe)	86
4	NiCl ₂ (dppf) ₂ instead of NiCl ₂ (dppe)	94
5	THF instead of Et ₂ O	42
6	1,4-dioxane instead of Et ₂ O	51
7	benzene instead of Et ₂ O	13
8	toluene instead of Et ₂ O	24
9	-78 °C → 0 °C (immediately)	91
10	-78 °C → -40 °C (gradually)	20
11	-40 °C → 0 °C (gradually)	97
12	0 °C → 30 °C (gradually)	94

^a Reactions were run using **6** (0.50 mmol), **11a** (0.75 mmol), and the catalyst (0.025 mmol) in the solvent (0.12 M). ^b NMR yields. ^c Isolated yields.

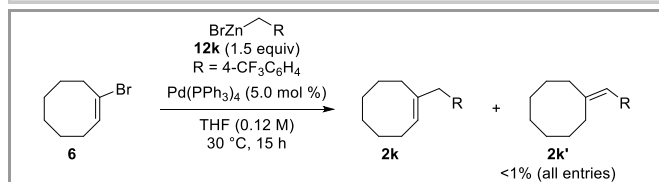
We first optimized the conditions for nickel-catalyzed cross-coupling using brominated CCO **6** and organomagnesium reagent **11a** (Table 1).¹³ The reaction was carried out using NiCl₂(dppe) as a catalyst in diethyl ether (Et₂O) at -78 °C, with a gradual increase to 0 °C, resulting in the formation of **2a** in 98% yield (Table 1, entry 1). As anticipated, **2a** was selectively obtained without yielding byproduct **2a'**. Consequently, **2a** was easily isolated with a yield of 90%. Other nickel catalysts proved to be useful as well (Table 1, entries 2–4). However, the other solvents we investigated exhibited lower efficiency (Table 1, entries 5–8). Increasing the reaction temperature to 0 °C was crucial, and this reaction showed no sensitivity to higher temperatures up to 30 °C (Table 1, entries 9–12).

Furthermore, we investigated the scope of organomagnesium reagents in the nickel-catalyzed cross-coupling of **6** under specified conditions using 5.0 mol % of NiCl₂(dppe) and 1.5 equivalent of **11** (Scheme 3). The solvent used for preparing each organomagnesium reagent, either tetrahydrofuran (THF) or Et₂O, was also used in the cross-coupling reactions. Electron-rich reagents yielded **2b** and **2c** in high yields. Benzyl metal reagents bearing methyl groups allowed the introduction of *para*-, *meta*-, *ortho*-methylbenzyl groups (**2d**, **2e**, and **2f**) and a 2,4,6-trimethylbenzyl group (**2g**). A naphthylmethyl group was also introduced (**2h**). Not only benzyl magnesium reagents but also phenyl- and phenethylmagnesium reagents were applicable (**2i** and **2j**). In all the cases, the products of **2** yielded exclusively without the formation of regioisomers **2'**.



Scheme 3 Scope of organomagnesium reagents in nickel-catalyzed cross-coupling of **6**

Table 2 Optimization for Cross-Coupling of **6** and **12k**^a

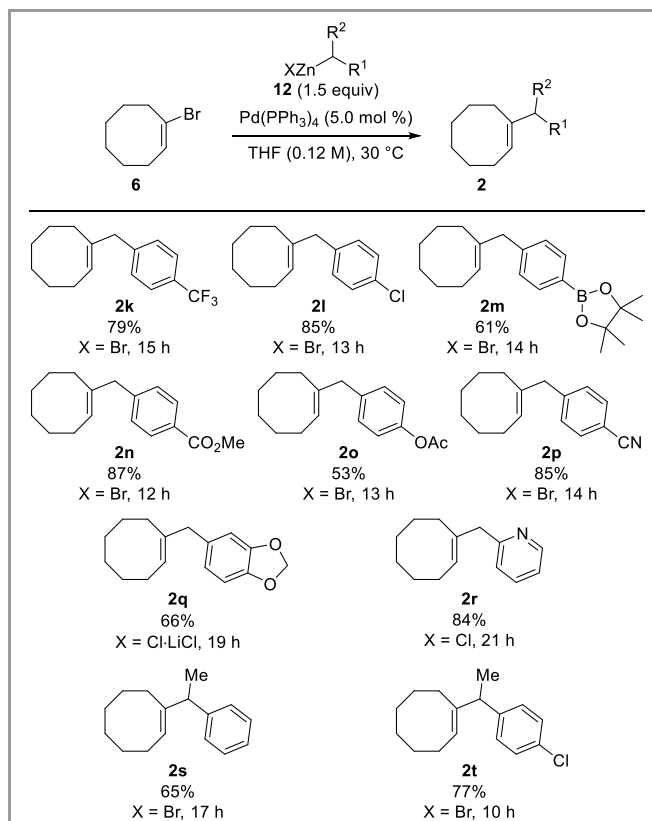


Entry	Deviation from the standard conditions	2k (%) ^b
1	none	99 (79 ^c)
2	60 °C	99
3	−78 °C → 0 °C (gradually)	<1
4	−78 °C → 0 °C (gradually) NiCl ₂ (dppe) ₂ instead of Pd(PPh ₃) ₄	<1

^a Reactions were run using **6** (0.50 mmol), **12k** (0.75 mmol), and Pd(PPh₃)₄ (0.025 mmol) in THF (0.12 M). ^b NMR yields. ^c Isolated yields.

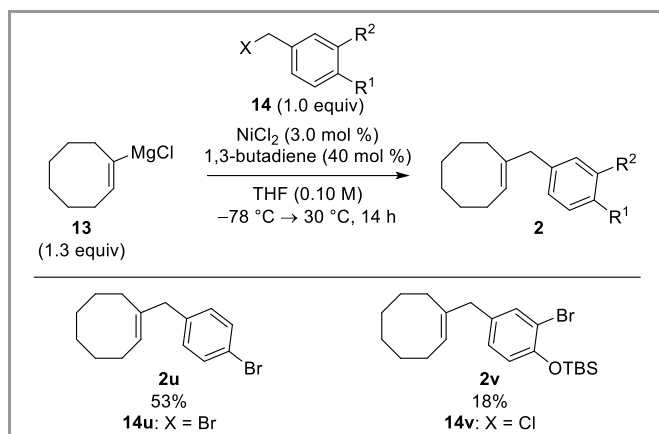
Because we were unable to prepare the corresponding benzylmagnesium reagent bearing a trifluoromethyl group, we proceeded to carry out cross-coupling using organozinc reagent **12k** (Table 2).¹⁴ A reaction of **6** using Pd(PPh₃)₄ as a catalyst in THF at 30 °C efficiently resulted in the formation of **2k** in 99% yield without the formation of **2k'** (Table 2, entry 1). The reaction

temperature was subsequently increased to 60 °C without any loss in yield (Table 2, entry 2); however, a lower temperature was less efficient (Table 2, entry 3). The nickel-catalyzed system was not useful in the cross-coupling of organozinc **12k** (Table 2, entry 4).



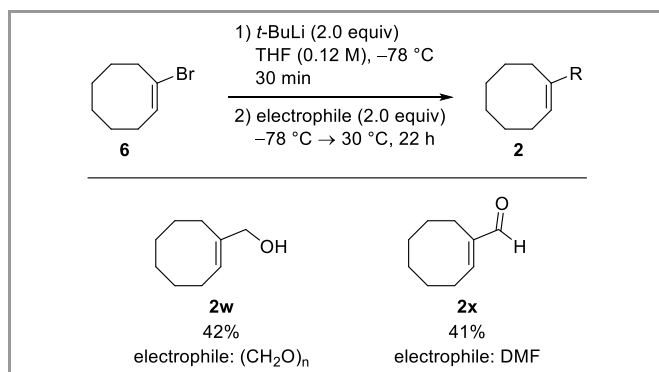
Scheme 4 Scope of organozinc reagents in palladium-catalyzed cross-coupling of **6**

We investigated the scope of organozinc reagents in the palladium-catalyzed cross-coupling of **6** under the specified conditions using 5.0 mol % of Pd(PPh₃)₄ and 1.5 equivalent of **12** (Scheme 4). Electron-deficient reagents were used to obtain **2k** and **2l** in high yields. A boronic acid ester was well accommodated under the conditions to yield **2m**, thereby facilitating additional derivatization. Taking advantage of the chemoselective reactivity of organozinc reagents, ester and cyano groups were tolerated, allowing for the formation of CCOs **2n**, **2o**, and **2p** with their electrophilic groups remaining intact. Heterocyclic substituents were introduced to obtain **2q** and **2r**, and CCOs **2s** and **2t** with a secondary alkyl group were also synthesized. In all the cases, products of **2** yielded selectively without the formation of regioisomers **2'**.

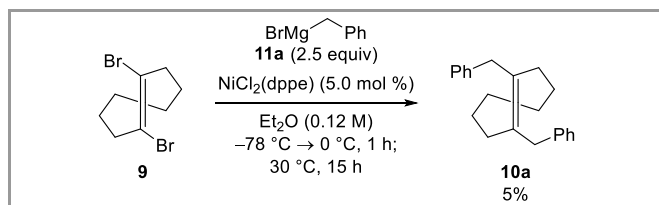


Scheme 5 Synthesis of the brominated-substituent-bearing CCOs

To synthesize CCOs with a halogen-group-bearing substituent, we reversed the roles of the electrophiles and nucleophiles. Following the methodology established by Kambe, Terao, et. al., we conducted the cross-coupling of cyclooctenyl-magnesium reagent **13** with electrophile **14** containing a halogen group (Scheme 5).¹⁵ Despite moderate yields, this strategy enabled the synthesis of CCOs **2u** and **2v**, which were inaccessible through the conventional synthetic methods depicted in Scheme 1.

Scheme 6 CCO synthesis through the lithiation of **6**

In addition to the cyclooctenyl-magnesium reagent, we demonstrated the utility of an analogous organolithium reagent to increase the synthetic flexibility. A cyclooctenyl-lithium reagent was prepared by lithiating bromocyclooctene **6** with *t*-butyllithium, and it was used for nucleophilic addition to carbonyl electrophiles (Scheme 6). Hydroxymethyl and formyl groups were introduced in the olefin moiety, yielding **2w** and **2x**, thus further expanding the variety of substituents.



Scheme 7 Synthesis of the 1,2-disubstituted TCO

Finally, a cross-coupling method was conducted to synthesize the substituted TCO. The nickel-catalyzed cross-coupling of dibrominated TCO **9** resulted in the formation of 1,2-disubstituted TCO **10a** (Scheme 7).¹⁶ Notably, the 1,2-

disubstituted TCO was synthesized for the first time, despite its low yield.¹⁷ Thus, we investigated the catalytic activity of **10a** toward the bromolactonization of **15** (Table 3). In our previous work, we developed monosubstituted TCOs as catalysts for bromolactonization (Table 3, entries 2 and 3),^{8a} in which we found the substituents of TCOs have significant effects on the catalytic activity, and we identified **17** bearing a benzyl group as the most active catalyst. The investigation of the catalytic efficiency of **10a** bearing two benzyl groups revealed that **10a** was superior to **17** (Table 3, entry 1). The present findings demonstrate that our synthetic methods expand the library of substituted cyclooctenes, leading to the development of high-performance molecules through the accumulation of functionalities in the substituents.

Table 3 Catalytic Activity of Substituted TCOs^a

Entry	Catalyst	Yield (%)
1	10a	99
2 ^b	17	88
3 ^b	none	3

^a Reactions were run using **15** (0.10 mmol), NBA (0.12 mmol), and the catalyst (0.010 mmol) in CH₂Cl₂ (1.0 mL). ^b Ref 8a.

In summary, we developed methods for introducing various substituents into the olefin moiety of cyclooctenes through cross-coupling reactions, thus synthesizing various 1-substituted CCOs. These methods unlocked new ways to synthesize previously inaccessible derivatives, thereby enabling the syntheses of CCOs bearing various functional groups including brominated substituents. These methods were also applied to the synthesis of a 1,2-disubstituted TCO for the first time, which was found to be a significantly active organocatalyst in relation to the previously developed monosubstituted TCO. We believe that the developed synthetic methods will accelerate further research in exploring functional molecules by the use of not only TCOs but also CCOs bearing functionalized substituents.

Funding Information

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology (JP21H05076, JP23H01953, and JP23K26646). K.A. also acknowledges Inoue Foundation for Science, Mizuho Foundation for the Promotion of Sciences, Japan Association for Chemical Innovation, Tobe Maki Scholarship Foundation, the NOVARTIS Foundation (Japan) for the Promotion of Science, the Kurata Grants by the Hitachi Global Foundation, the Inamori Foundation, and the Society of Iodine Science. R.M. also acknowledges the Japan Society for the Promotion of Science for Young Scientists for the fellowship support (JP21J23149).

Acknowledgment

We thank Technical Division of Institute for Catalysis, Hokkaido University, for technical support.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

- (1) *The Chemistry of Double-Bonded Functional Groups*, Vol. 2; Patai, S. Ed.; John Wiley & Sons: Chichester; New York; Brisbane; Toronto; Singapore, 1989.
- (2) For selected reviews, see: (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (b) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31. (c) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204. (d) Nagamoto, M.; Nishimura, T. *ACS Catal.* **2017**, *7*, 833.
- (3) Blomquist, A. T.; Liu, L. H.; Bohrer, J. C. *J. Am. Chem. Soc.* **1952**, *74*, 3643.
- (4) For reviews, see: (a) Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213. (b) Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* **1984**, *125*, 1. (c) Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27. (d) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley, New York, 1994, pp 1172–1175.
- (5) For isolation of optically active forms, see: (a) Cope, A. C.; Howell, C. F.; Knowles, A. J. *Am. Chem. Soc.* **1962**, *84*, 3190. (b) Cope, A. C.; Ganellin, C. R.; Johnson, H. W., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3191. (c) Cope, A. C.; Ganellin, C. R.; Johnson, H. W., Jr.; Van Auken, T. V.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1963**, *85*, 3276. (d) Cope, A. C.; Mehta, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 5626. (e) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644. (f) Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3649. For selected examples of enantioselective syntheses, see: (g) Inoue, Y.; Yokoyama, T.; Yamasaki, N.; Tai, A. *Nature* **1989**, *341*, 225. (h) Tomooka, K.; Uehara, K.; Nishikawa, R.; Suzuki, M.; Igawa, K. *J. Am. Chem. Soc.* **2010**, *132*, 9232. (i) Igawa, K.; Ichikawa, N.; Ano, Y.; Katanoda, K.; Ito, M.; Akiyama, T.; Tomooka, K. *J. Am. Chem. Soc.* **2015**, *137*, 7294. (j) Miura, T.; Nakamuro, T.; Liang, C.-J.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 15905. (k) Okayama, Y.; Tsuji, S.; Toyomori, Y.; Mori, A.; Arae, S.; Wu, W.-Y.; Takahashi, T.; Ogasawara, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 4927.
- (6) For selected examples of the use as chiral synthetic intermediates, see: (a) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182. (b) Tomooka, K.; Suzuki, M.; Uehara, K.; Shimada, M.; Akiyama, T. *Synlett* **2008**, 2518. (c) Tomooka, K.; Akiyama, T.; Man, P.; Suzuki, M. *Tetrahedron Lett.* **2008**, *49*, 6327. (d) Tomooka, K.; Iso, C.; Uehara, K.; Suzuki, M.; Nishikawa-Shimono, R.; Igawa, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 10355. (e) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954. (f) Royzen, M.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3760. (g) Hurlocker, B.; Hu, C.; Woerpel, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 4295.
- (7) For selected examples, see: (a) Thalhammer, F.; Wallfahner, U.; Sauer, J. *Tetrahedron Lett.* **1990**, *31*, 6851. (b) Blackman, M. L.; Royzen, M.; Fox, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 13518. (c) Devaraj, N. K.; Weissleder, R. *Acc. Chem. Res.* **2011**, *44*, 816. (d) Liu, F.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 11483. (e) Kamber, D. N.; Liang, Y.; Blizzard, R. J.; Liu, F.; Mehl, R. A.; Houk, K. N.; Prescher, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 8388.
- (8) (a) Einaru, S.; Shitamichi, K.; Nagano, T.; Matsumoto, A.; Asano, K.; Matsubara, S. *Angew. Chem., Int. Ed.* **2018**, *57*, 13863. (b) Nagano, T.; Einaru, S.; Shitamichi, K.; Asano, K.; Matsubara, S. *Eur. J. Org. Chem.* **2020**, 7131.
- (9) Murata, R.; Shitamichi, K.; Hiramatsu, M.; Matsubara, S.; Uruguchi, D.; Asano, K. *Chem.—Eur. J.* **2024**, *30*, e202303399.
- (10) (a) Vedejs, E.; Snoble, K. A. J.; Fuchs, P. L. *J. Org. Chem.* **1973**, *38*, 1178. (b) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044.
- (11) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.
- (12) (a) *Metal Catalyzed Cross-Coupling Reactions and More*, 1st ed.; de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley-VCH, 2013. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
- (13) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958.
- (14) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
- (15) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.
- (16) Synthesis of a monobrominated TCO was failed, and its cross-coupling could not be investigated.
- (17) Full of **9** was converted, providing several products, although the by-products were not identified. The stability of **10a** is sufficient for isolation.