Synlett C.-H. Liu, Z.-X. Yu Cluster

# Rh(I)-Catalyzed Intramolecular [3+2] Cycloaddition of *trans*-2-Allene-Vinylcyclopropanes

**Cheng-Hang Liu**
**Zhi-Xiang Yu***

Beijing National Laboratory for Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, P. R. of China
yuzx@pku.edu.cn

Published as part of the Cluster C–C Activation

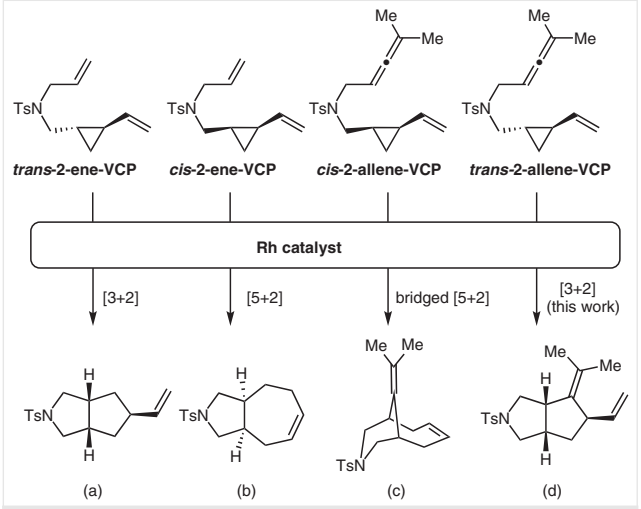

Received: 13.11.2017
Accepted after revision: 09.01.2017
Published online: 18.01.2018
DOI: 10.1055/s-0037-1609199; Art ID: st-2017-u0830-c

**Abstract** An intramolecular [3+2] cycloaddition of *trans*-2-allene-vinylcyclopropanes for the synthesis of bicyclo[3.3.0]octane derivatives is developed.

**Key words** allenes, vinylcyclopropanes, rhodium, [3+2] cycloaddition, bicyclo[3.3.0]octanes

Five-membered carbocyclic rings are ubiquitous in natural products of biological and pharmaceutical importance. Consequently, many powerful synthetic methodologies for the construction of five-membered rings have been developed.[1] Among these methodologies, [3+2] cycloadditions[2] between various three-carbon and two-carbon synthons are efficient for the construction of five-membered rings. Cyclopropanes, being small rings with high strain, have been reported as good three-carbon synthons and various cyclopropane derivatives substituted with different activating functional groups, such as cyclopropyl ketones,[3a–e] cyclopropyl carboxamide,[3f] cyclopropenones[4] and alkylidenecyclopropanes (ACPs),[5,6] have been successfully used in [3+2] cycloadditions.

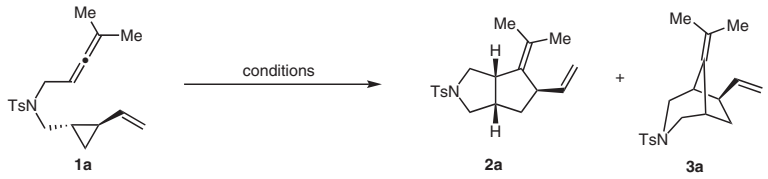
Our group has a strong interest in discovering and developing transition-metal-catalyzed cycloadditions using highly strained small rings. We found previously that vinylcyclopropanes (VCPs),[7] without electron-withdrawing activation groups, could also play the role of three-carbon synthons in intramolecular cycloadditions.[8,9] For example, in 2008, we reported the intramolecular [3+2] cycloaddition of *trans*-2-ene-VCPs to afford fused bicyclic products (Scheme 1, a).[8a]




**Scheme 1** Reaction modes of 2-ene/allene-VCPs under Rh(I) catalysis

When we used *cis*-2-ene-VCPs as substrates, unexpected intramolecular [5+2] cycloaddition took place, although limited examples were reported (Scheme 1, b).[8a] To overcome the drawback of such a [5+2] reaction with narrow substrate scope, we changed the 2π component from alkenes to allenes, which were expected to have high reactivity,[10] and observed an unanticipated bicyclo[4.3.1]decane product via a novel bridged [5+2] reaction (Scheme 1, c).[11] Inspired by these studies, we synthesized *trans*-2-allene-VCPs and investigated which reaction, i.e., the [3+2] or the bridged [3+2] cycloaddition, would occur with these substrates.

**Table 1** Optimization of the Rhodium(I)-Catalyzed Intramolecular [3+2] Cycloaddition[a]




**1a** **2a** **3a**

| Entry | Catalyst | Solvent | Temp (°C) | Time (h) | Yield (%)[b] | Ratio (**2a**:**3a**)[c] |
|---|---|---|---|---|---|---|
| 1 | $[Rh(CO)_2Cl]_2$ | DME | 80 | 4 | 84 | 1:1.8 |
| 2 | $[Rh(COD)Cl]_2$ | DME | 80 | 5 | NR | – |
| 3 | $[Rh(COE)_2Cl]_2$ | DME | 80 | 6 | 36 | 2:1[d] |
| 4 | $Rh(CO)(PPh_3)_2Cl$ | DME | 80 | 28 | trace | – |
| 5 | $Rh(PPh_3)_3Cl$ | DME | 80 | 17 | trace | – |
| 6 | $[Rh(CO)_2Cl]_2$/10 mol% AgOTf | DME | 80 | 5 | 22 | 9:1 |
| 7 | $[Rh(COE)_2Cl]_2$/10 mol% AgOTf | DME | 80 | 5 | dec. | – |
| 8 | $Rh(PPh_3)_3Cl$/5 mol% AgOTf | DME | 80 | 7 | 76 | 1.4:1 |
| 9 | $Rh(CO)(PPh_3)_2Cl$/5 mol% AgOTf | DME | 80 | 5 | 68 | 4.2:1 |
| 10 | $Rh(CO)(PMe_3)_2Cl$/5 mol% AgOTf | DME | 80 | 16 | 51 | >20:1 |
| **11** | **$Rh(CO)(PMe_3)_2Cl$/5 mol% AgOTf** | **DCE** | **80** | **20** | **74** | **>20:1** |
| 12 | $Rh(CO)(PMe_3)_2Cl$/5 mol% AgOTf | toluene | 80 | 16 | 66 | >20:1 |
| 13 | $Rh(CO)(PMe_3)_2Cl$/5 mol% AgOTf | dioxane | 80 | 16 | 60 | >20:1 |
| 14 | $Rh(CO)(PMe_3)_2Cl$/5 mol% $AgSbF_6$ | DCE | 80 | 24 | 44 | 20:1 |
| 15 | $Rh(CO)(PMe_3)_2Cl$/5 mol% $AgNTf_2$ | DCE | 80 | 24 | 60 | >20:1 |
| 16 | $Rh(CO)(PMe_3)_2Cl$/5 mol% AgOTf | toluene | 100 | 3 | 76 | 17:1 |

[a] Reactions were performed on 0.1 mmol scale with 5 mol% of the Rh catalyst.
[b] Combined isolated yield of **2a** and **3a**. NR = no reaction; dec. = decomposed.
[c] The ratio was determined by $^1H$ NMR.
[d] Obtained with an inseparable, unidentified by-product.

Our test of the new design started with the tosylamide-tethered *trans*-2-allene-VCP substrate **1a** (Table 1). At first, we tried $[Rh(CO)_2Cl]_2$ as the catalyst, which was used in the previous bridged [5+2] reaction,[11] finding that fused bicyclic product **2a** and bridged [3+2] cycloadduct **3a** were both produced in a combined yield of 84% with a ratio of **2a**/**3a** of 1:1.8 (entry 1). Other rhodium catalysts, such as $[Rh(COD)Cl]_2$ and Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$ were also tested, but only trace products were observed in most cases (entries 2–5). The situation took a favored turn when we employed cationic Rh(I) catalysts. The fused bicyclic [3+2] product **2a** became the main product (ratio of **2a**/**3a** = 9:1) when $[Rh(CO)_2Cl]_2$/AgOTf was used as the catalyst, although the yield was rather poor (entry 6). $[Rh(COE)_2Cl]_2$/AgOTf proved to be inefficient because decomposition of the starting material was observed in this case (entry 7). A series of cationic Rh(I) catalysts with phosphine ligands was also tested (entries 8–10), and $Rh(CO)(PMe_3)_2Cl$[12]/AgOTf showed the best selectivity (**2a**/**3a** > 20:1) with a yield of 51%. The skeleton of the product **2a** was further confirmed by single-crystal X-ray crystallographic analysis (Figure 1).[13]

Next, we screened other solvents (Table 1, entries 11–13) and silver salts (entries 14 and 15). DCE proved to be the best solvent and a yield of 74% was achieved without any decrease of the selectivity. When $AgSbF_6$ or $AgNTf_2$ was used instead of AgOTf, slightly lower yields were obtained. Finally, we increased the reaction temperature to 100 °C, finding that the reaction yield was nearly the same, but that the ratio of **2a**/**3a** decreased to 17:1.

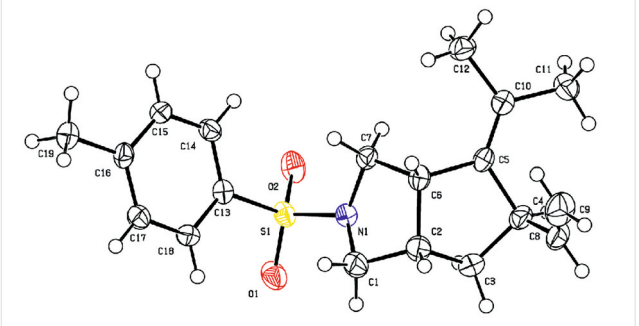
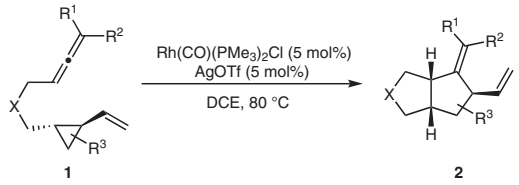
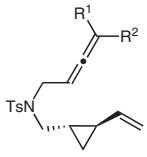
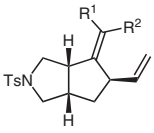
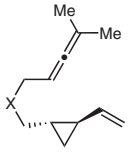
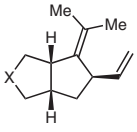
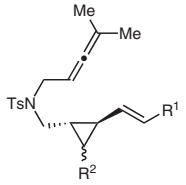
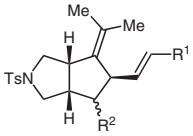



**Figure 1** ORTEP representation of compound **2a**

**Table 2** Substrate Scope of the Intramolecular [3+2] Cycloaddition[a]




1 2

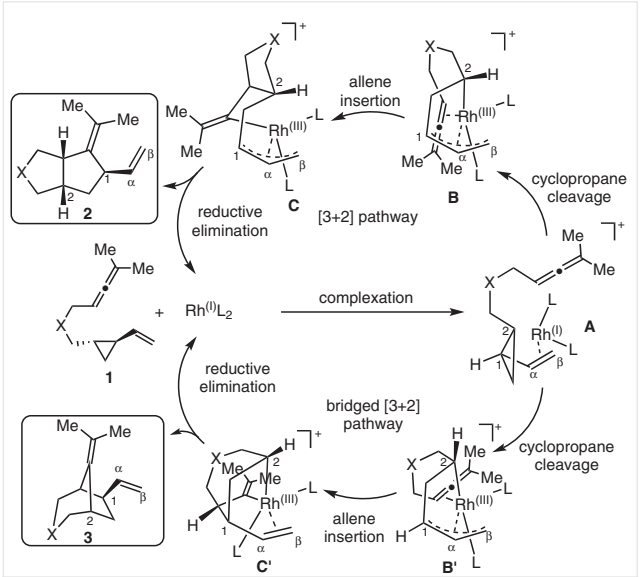
| Entry | Substrate | Product, Time, Yield[b] |
|---|---|---|
| |  |  |
| 1 | **1a**, $R^1 = R^2$ = Me | **2a**, 20 h, 73% |
| 2 | **1b**, $R^1 = R^2$ = Et | **2b**, 20 h, 73% |
| 3 | **1c**, $R^1 = R^2$ = –$CH_2(CH_2)_4CH_2$– | **2c**, 20 h, 73% |
| 4 | **1d**, $R^1 = R^2$ = –$CH_2(CH_2)_3CH_2$– | **2d**, 20 h, 62% |
| 5 | **1e**, $R^1$ = Me, $R^2$ = Ph | **2e**, 20 h, 68% (*Z*/*E* = 1.2:1)[c] |
| |  |  |
| 6 | **1f**, X = NNs | **2f**, 20 h, 80% |
| 7 | **1g**, X = NBs | **2g**, 18 h, 76% |
| 8 | **1h**, X = $NSO_2Ph$ | **2h**, 20 h, 76% |
| 9 | **1i**, X = $C(CO_2Me)_2$ | no reaction |
| |  |  |
| 10 | **1j**, $R^1$ = Ph, $R^2$ = H | complex mixture |
| 11 | **1k**, $R^1$ = Et, $R^2$ = H | complex mixture |
| 12 | **1l**, $R^1$ = H, $R^2$ = Me (dr = 1.4:1) | **2l**, 20 h, 72% (dr = 1.4:1)[c] |

[a] Reactions were performed on 0.2 mmol scale and DCE (4 mL) was used as the solvent.
[b] Yield given as an average of two runs.
[c] The two isomers were inseparable and the ratio was determined by $^1$H NMR.

We chose the conditions in entry 11 of Table 1 as the optimum reaction conditions,[14] and began to investigate the reaction scope of the present [3+2] cycloaddition (Table 2). Firstly, terminally disubstituted allenes were found to be excellent substrates (entries 1–5) and fused bicyclic products **2a–e** were isolated in good yields. For substrate **1e**, which had two different terminal substituents on the allene moiety, product **2e** was obtained in 68% yield with a *Z*/*E* ratio of 1.2:1. In addition to using NTs-tethered substrates, NNs-, NBs- and $NSO_2Ph$-tethered substrates were also synthesized and tested in [3+2] reactions under the optimized reaction conditions (entries 6–8). Good yields were achieved for all these substrates in [3+2] cycloadditions. Unfortunately, C-tethered substrate **1i** was not converted into the desired [3+2] cycloadduct because no reaction took place under the optimized conditions (entry 9).

We also synthesized substrates **1j–l** and examined how the substituents on the VCP moieties of the substrates affected the reaction outcomes (Table 2, entries 10–12). Our experiments showed that the present [3+2] cycloaddition was sensitive to changes of the VCP moieties of the substrates. When substrate **1l** with substitution on the cyclopropane moiety was used, a good yield was achieved. However, when substrates **1j** and **1k** with substituents on the alkene moieties were tested, complex mixtures were generated. For substrate **1k**, a low yield of the corresponding bicyclic product was observed by NMR of the crude material; however, we were unable to isolate the product in pure form due to the presence of some inseparable, unidentified by-products.

The proposed mechanisms of this [3+2] cycloaddition and its competing bridged [3+2] reaction are shown in Scheme 2.




**Scheme 2** Plausible catalytic cycles of the [3+2] reactions

The [3+2] catalytic cycle commences with the binding of the catalytic rhodium species to the alkene moiety of the VCP to give intermediate **A**, followed by cleavage of the cyclopropane ring. When $Rh(CO)(PMe_3)_2Cl$/AgOTf is used as the catalyst, intermediate **B** is generated. Next, the internal double bond of the allene inserts into the Rh–C2 bond. Fi-

nally, the fused bicyclic product **2** is formed by reductive elimination and the catalytic rhodium species is regenerated to complete the catalytic cycle. Here, the *trans* configuration of the VCP in substrate **1** makes the allene moiety stay near the carbon atom C1, leading to the [3+2] cycloadduct **2**[15] instead of the [5+2] cycloadduct. However, when $[Rh(CO)_2Cl]_2$ is used, both [3+2] and bridged [3+2] pathways are possible. In this case, generation of intermediate **B′** becomes more favored, and this step is followed by insertion of the allene's internal double bond into the Rh–C1 bond, but in an opposite manner compared to the normal [3+2] pathway. The bridged [3+2] cycloadduct **3** is finally generated by reductive elimination from intermediate **C′**. Similarly, the allene moiety stays near the carbon atom C1 because of the *trans* configuration of the VCP in the substrate **1**, leading to bridged [3+2] cycloadduct **3** instead of the bridged [5+2] cycloadduct.

In conclusion, an intramolecular [3+2] cycloaddition of *trans*-2-allene-vinylcyclopropanes has been developed to synthesize bicyclo[3.3.0]octane derivatives. The formation of 1,4-diene moieties in the products enables further access to more complex structures.[16]

## Funding Information

We thank the National Natural Science Foundation of China (21672008) for financial support.

## Acknowledgment

We thank Prof. Dr. Wen-Xiong Zhang and Dr. Neng-Dong Wang for X-ray crystal analysis. We also thank Mr. Tian-Hao Gao of Peking University for experimental assistance.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609199.

## References and Notes

(1) Reviews involving the construction of five-membered rings: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Chen, P.-h.; Billett, B. A.; Tsukamoto, T.; Dong, G. *ACS Catal.* **2017**, *7*, 1340. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404. (d) Nishiwaki, N. *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Wiley-VCH: Hoboken, **2014**. (e) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845.

(2) Selected examples of [3+2] cycloadditions: (a) Wilson, J. E.; Fu, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1426. (b) Wei, Y.; Shi, M. *Org. Chem. Front.* **2017**, *4*, 1876. (c) Trost, B. M.; Stambuli, J. P.; Silverman, S. M.; Schwörer, U. *J. Am. Chem. Soc.* **2006**, *128*, 13328. (d) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (e) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166. (f) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (g) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 7506.

(3) (a) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348. (b) Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 6788. (c) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350. (d) Liu, L.; Montgomery, J. *Org. Lett.* **2007**, *9*, 3885. (e) Tamaki, T.; Ohashi, M.; Ogoshi, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 12067. (f) Liu, Q.-S.; Wang, D.-Y.; Yang, Z.-J.; Luan, Y.-X.; Yang, J.-F.; Li, J.-F.; Pu, Y.-G.; Ye, M. *J. Am. Chem. Soc.* **2017**, *139*, 18150.

(4) Wender, P. A.; Paxton, T. J.; Williams, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 14814.

(5) (a) Lewis, R. T.; Motherwell, W. B.; Shipman, M. *J. Chem. Soc., Chem. Commun.* **1988**, 948. (b) Bapuji, S. A.; Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1989**, *30*, 7107. (c) Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1991**, *32*, 1103. (d) Lautens, M.; Ren, Y.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8821. (e) Lautens, M.; Ren, Y.; Delanghe, P.; Chiu, P.; Ma, S.; Colucci, J. *Can. J. Chem.* **1995**, *73*, 1251. (f) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597. (g) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 10668. (h) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203.

(6) (a) Yao, B.; Li, Y.; Liang, Z.; Zhang, Y. *Org. Lett.* **2011**, *13*, 640. (b) Kuila, B.; Mahajan, D.; Singh, P.; Bhargava, G. *Tetrahedron Lett.* **2015**, *56*, 1307.

(7) Examples of VCPs that contain strong electron-withdrawing groups: (a) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825. (b) Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 4474. (c) Trost, B. M.; Morris, P. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 6167. (d) Hiroi, K.; Yamada, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1835. (e) Mei, L.-y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2012**, *31*, 7591. (f) Trost, B. M.; Morris, P. J.; Sprague, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 17823. (g) Halskov, K. S.; Næsborg, L.; Tur, F.; Jørgensen, K. A. *Org. Lett.* **2016**, *18*, 2220. (h) Tombe, R.; Iwamoto, T.; Kurahashi, T.; Matsubara, S. *Synlett* **2014**, *25*, 2281.

(8) [3+2] Cycloaddition of VCPs: (a) Jiao, L.; Ye, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2008**, *130*, 7178. (b) Jiao, L.; Lin, M.; Yu, Z.-X. *Chem. Commun.* **2010**, *46*, 1059. (c) Li, Q.; Jiang, G.-J.; Jiao, L.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 1332. (d) Jiao, L.; Lin, M.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 447. (e) Lin, M.; Kang, G.-Y.; Guo, Y.-A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2012**, *134*, 398. (f) Jiao, L.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78*, 6842.

(9) [3+2] Cycloaddition of vinyl aziridines: (a) Lin, T.-Y.; Zhu, C.-Z.; Zhang, P.; Wang, Y.; Wu, H.-H.; Feng, J.-J.; Zhang, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 10844. (b) Feng, J.-J.; Lin, T. Y.; Zhu, C. Z.; Wang, H.; Wu, H.-H.; Zhang, J. *J. Am. Chem. Soc.* **2016**, *138*, 2178.

(10) Yu, Z.-X.; Cheong, P. H.-Y.; Liu, P.; Legault, C. Y.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 2378.

(11) Liu, C.-H.; Yu, Z.-X. *Angew. Chem. Int. Ed.* **2017**, *56*, 8667.

(12) $Rh(CO)(PMe_3)_2Cl$ was synthesized according to the following report: Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938.

(13) CCDC 1562354 (**2a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(14) **Intramolecular [3+2] Cycloaddition; Typical Procedure**
To a mixture of $Rh(CO)(PMe_3)_2Cl$ (3.2 mg, 0.01 mmol, 5 mol%) and AgOTf (2.6 mg, 0.01 mmol, 5 mol%) was added DCE (2 mL) and the mixture was stirred at room temperature under argon for 5 min. A solution of **1a** (0.2 mmol) in DCE (2 mL) was added

at room temperature, and the resulting solution was immersed into a preheated oil bath and stirred at 80 °C. After 20 h, the reaction mixture was cooled to room temperature and concentrated. The crude product was purified by flash column chromatography on silica gel to afford the [3+2] cycloadduct **2a**. Run 1: **1a** (67.5 mg) was converted into **2a** (49.8 mg), yield 74%. Run 2: **1a** (66.7 mg) was converted into **2a** (48.1 mg), yield 72%. So, the average yield of two runs was 73%; white solid; mp 99–102 °C; $R_f$ = 0.59 (PE/EtOAc, 5:1); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 5.65 (ddd, *J* = 17.0, 10.2, 6.3 Hz, 1 H), 4.90 (m, 1 H), 4.83 (m, 1 H), 3.53–3.43 (m, 1 H), 3.34–3.25 (m, 1 H), 3.24–3.14 (m, 2 H), 3.14–3.05 (m, 1 H), 2.95 (dd, *J* = 9.5, 7.3 Hz, 1 H), 2.71–2.58 (m, 1 H), 2.44 (s, 3 H), 1.69 (dd, *J* = 12.5, 6.9 Hz, 1 H), 1.62 (s, 3 H), 1.58 (s, 3 H), 1.56–1.48 (m, 1 H); $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 143.3, 139.7 (+), 138.1, 133.2, 129.5 (+, 2 C), 127.6 (+, 2 C), 127.4, 112.9 (–), 52.8 (–), 52.2 (–), 47.1 (+), 45.8 (+), 41.7 (+), 36.8 (–), 22.0 (+), 21.5 (+), 21.0 (+), DEPT explanation in SI. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{26}NO_2S$: 332.1679; found: 332.1670.

(15) A rationalization of [3+2] and [5+2] cycloadditions has been given in our previous publication, see Ref. 8a.

(16) (a) Lee, D.-Y.; Kim, I.-J.; Jun, C.-H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3031. (b) Xu, G.; Renaud, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 3657. (c) Trost, B. M.; Hansmann, M. M.; Thaisrivongs, D. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 4950. (d) Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R.; Martin-Fontecha, M.; El-Boulifi, N.; Duran-Sampedro, G.; Enma, D. *Org. Lett.* **2009**, *11*, 4148. (e) Eilbracht, P.; Balß, E.; Acker, M. *Chem. Ber.* **1985**, *118*, 825.