Tetrahedron Letters 54 (2013) 512–514

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Palladium(II)-catalyzed asymmetric cycloisomerization of enynes for axially chiral biaryl construction

Nobuaki Kadoya, Masato Murai, Masako Ishiguro, Jun'ichi Uenishi, Motokazu Uemura *

*Kyoto Pharmaceutical University, Kyoto 607-8412, Japan*

ARTICLE INFO

*Article history:*
Received 1 October 2012
Revised 15 November 2012
Accepted 19 November 2012
Available online 24 November 2012

*Keywords:*
Axially chiral biaryl
Asymmetric cycloisomerization
Enyne compounds
Palladium catalyst

ABSTRACT

Palladium(II)-catalyzed asymmetric cycloisomerization of enynes with (*R*)-binap gave axially chiral biaryls with up to 99%ee. The reactivity and enantioselectivity depended on the nature and position of substituent of the arene ring. The enynes with *ortho* methoxy arene at alkyne terminus gave chiral biaryls with good enantioselectivity.



Axially chiral biaryls are valuable compounds as chiral ligands or auxiliaries in asymmetric reaction, and also for biologically active natural products. There is a considerable current interest in the development of efficient methodologies for the synthesis of axially chiral biaryls.[1] Catalytic asymmetric synthesis of the axially chiral biaryls has been dramatically increased. Asymmetric biaryl coupling such as Suzuki,[2] Kumada,[3] and Negishi[4] coupling is achieved with high enantioselectivity in some cases. Asymmetric aromatization through transition-metal catalyzed [2+2+2]-cycloadditions of dienynes with alkynes or nitriles has also been a powerful method for axially chiral biaryl construction. For this purpose, Co(I),[5] Ir(I),[6] and Rh(I)[7] complexes with chiral ligands have been utilized for asymmetric cycloadditions. On the other hand, metal-catalyzed cycloisomerization of enyne compounds leading to carbocycles and heterocycles has been actively investigated. (*o*-Alkynyl)styrenes afforded functionalized naphthalenes via the 6-*endo* reaction pathway with gold(I) catalyst in good yields.[8] We previously reported that achiral gold(I)-catalyzed cycloisomerization of the planar chiral alkynyl arene chromium complexes bearing a styrene unit afforded diastereoselectively axially chiral biaryl chromium complexes, which were converted into chromium-free axial biaryls by demetallation.[9] Although the axially chiral biaryls could be obtained with high optical purity in this methodology, a most problematic limitation is access to the enantiomerically pure (arylhalide)$Cr(CO)_3$ complex as a starting material.[10] And, this procedure is a diastereoselective reaction utilizing the planar chiral arene chromium complex. Herein, we would like to report an asymmetric version of metal-catalyzed cycloisomerization of the corresponding chromium-free enyne compounds for axially chiral biaryls.

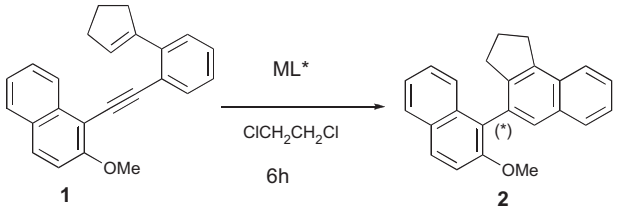
Initial efforts have focused on the optimization of an efficient system of the metal-catalyzed asymmetric reaction starting from 1-((2-cyclopentenylphenyl)ethynyl)-2-methoxynaphthalene (**1**) as a model substrate (Table 1). Among the surveys of a variety of metal catalysts,[11,12] cationic Au(I) catalysts showed a high catalytic activity for the cycloisomerization of enyne **1** at room temperature giving axially chiral biaryl compound **2** in good yield, but the enantioselectivity of **2** was only 15%ee (entry 1). A combination of chloro(1,5-cyclooctadiene)rhodium(I) dimer with $AgSbF_6$ gave no cycloisomerization product (entry 2). An isolated cationic rhodium catalyst at 60 °C was also ineffective (entry 3). Moreover, palladium(0) and palladium(II) acetate resulted in no cycloisomerization reaction (entries 4, 5). Fortunately, tetrakis(acetonitrile)-palladium(II) tetrafluoroborate in the presence of (*R*)-binap at 80 °C in 1,2-dichloroethane afforded the axially chiral biaryl **2** in 90% yield with 53%ee (entry 6).

This cationic Pd(II) catalyst is more Lewis acidic and can enhance the coordinating ability with the triple bond. Although the related *N*-alkenyl arylethynylamides were smoothly converted into chiral aryl 2-pyridone derivatives at room temperature by metal-catalyzed cycloisomerization,[13] the enyne compound **1** is required to heat for the cyclization. As the central bond rotation of the biaryl compound **2** would occur under the thermal conditions, we next examined an optimum reaction temperature for the achievement of higher ee value. The enantioselectivity of the cycloisomerization product **2** increased to 84%ee at 60 °C, although the chemical yield decreased to 52% (entry 7). At 50 °C, the enantiomeric excess was

* Corresponding author. Tel.: +81 75 595 4666; fax: +81 75 595 4763.
*E-mail address:* muemura@mb.kyoto-phu.ac.jp (M. Uemura).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.071

**Table 1**
Screening of asymmetric cycloisomerization




1 2

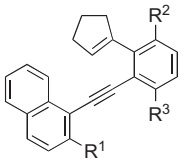
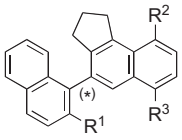
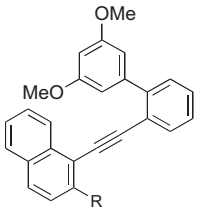
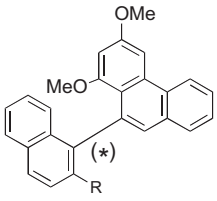
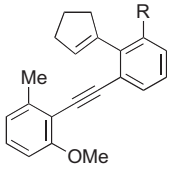
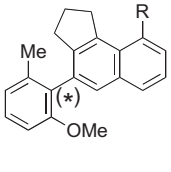
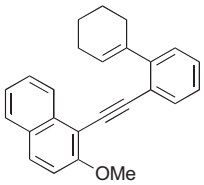
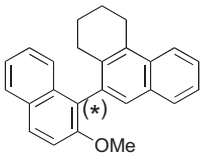
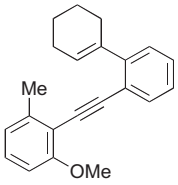
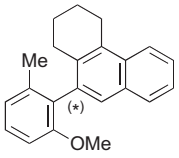
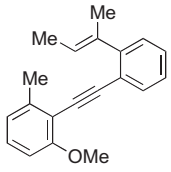
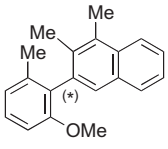
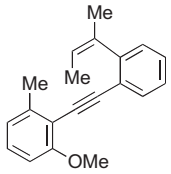
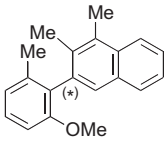
| Entry | ML* | Temp (°C) | Yield (%ee) |
|---|---|---|---|
| 1[a] | $[Au_2(R)\text{-binap}]Cl_2$], $AgNTf_2$ | Rt | 95 (15) |
| 2 | $[Rh(COD)Cl]_2$, $AgSbF_6$, (*R*)-binap | Rt | 0 (–) |
| 3 | $[Rh(COD)(R)\text{-binap}](BF_4)$ | 60 | 0 (–) |
| 4 | $Pd_2(dba)_3$, (*R*)-binap | 80 | 0 (–) |
| 5 | $Pd(OCOCF_3)_2$, (*R*)-binap | 80 | 0 (–) |
| 6[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-binap | 80 | 90 (53) |
| 7[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-binap | 60 | 52 (84) |
| 8[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-binap | 50 | 50 (84) |
| 9[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-xylylbinap | 60 | 10 (54) |
| 10[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-segphos | 60 | 8 (73) |
| 11[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-tolbinap | 60 | 17 (81) |
| 12[b] | $[Pd(MeCN)_4](BF_4)_2$, (*R*)-$H_8$-binap | 60 | 41 (70) |

[a] The reaction was performed using 5 mol % of gold catalyst and 10 mol % of Ag salt in $CH_2Cl_2$.
[b] The reaction condition is 5 mol % of palladium catalyst and 6–10 mol % of chiral ligand.

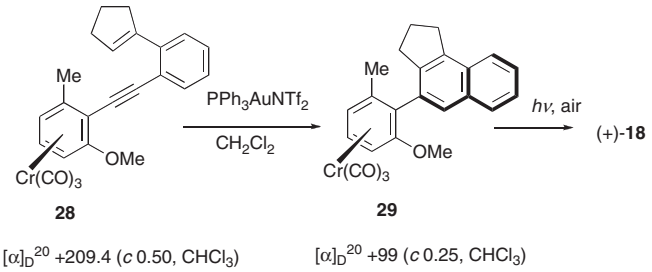
nearly equal to that of the conditions at 60 °C. This fact indicates that no central bond rotation of the axially chiral biaryl **2** takes place under the reaction conditions of lower temperature than 60 °C. With other chiral ligands, any advantages concerning both the yield and enantiomeric excess of compound **2** were not observed (entries 9–13).

Under these optimized conditions using $[Pd(MeCN)_4](BF_4)_2$ catalyst and (*R*)-binap, we next explored the scope of the asymmetric cycloisomerization with a modification of the substituent on the arene rings (Table 2). 2-Methylnaphthyl substituted enyne compound **7** gave no cycloisomerization product **8** under these conditions (entry 4). We anticipated that the enyne compounds possessing an electron rich arene or alkene should be required for the achievement of cycloisomerization. Therefore, an electron-donating MeO group was introduced on the phenyl ring for an enhancement of the electron-density. 2-Cyclopentenyl-3-methoxyphenyl substituted enyne compound **9** gave expectedly cycloisomerization product **10** in good yield, albeit the product was racemic (entry 5). For the asymmetric induction in the palladium-catalyzed cycloisomerization, the methoxy group at the neighboring position of the triple bond is an important factor.[13] A coordination structure of the cationic palladium(II) metal with methoxy group would induce a rigid environment in the asymmetric cycloisomerization. But, the regioisomeric 6-methoxyphenyl substituted enyne compound **11** afforded no cyclization product (entry 6). Lower ee value in entry 3 compared with the value of entry 2 would have contributed to form two different coordination intermediates of the palladium with methoxy group in compound **5**. Next, the asymmetric cycloisomerization of electron-rich arene substituted alkynes as a nucleophile was examined. 3′,5′-Dimethoxylbiphenyl substituted alkynes **13** and **15** gave cycloisomerization products **14** and **16**, respectively, with modest to good enantiomeric excesses (entries 7, 8). With 1-methoxy-3-methylphenyl substituted enyne compounds **17**, **19**, and **23**, the cycloisomerization products **18**, **20**, and **24** were obtained with higher enantiomeric excess values than 2-methoxynaphthyl substituted enyne analogs (entries 9, 12, 13). Particularly, 2-((2-cyclopentenylphenyl)ethynyl)-1-methoxy-3-methylbenzene (**17**) gave an excellent

**Table 2**
Cationic palladium(I)-catalyzed asymmetric cycloisomerization of enyne compounds with (*R*)-binap[a]

| Entry | Enyne compound | Product | Yield (%ee) |
|---|---|---|---|
| |  |  | |
| 1 | **1**: $R^1$ = OMe, $R^2$ = $R^3$ = H | **2** | 52 (84) |
| 2 | **3**: $R^1$ = $R^2$ = OMe, $R^3$ = H | **4** | 88 (82) |
| 3 | **5**: $R^1$ = $R^3$ = OMe, $R^2$ = H | **6** | 90 (49) |
| 4 | **7**: $R^1$ = Me, $R^2$ = $R^3$ = H | **8** | 0 (–) |
| 5 | **9**: $R^1$ = Me, $R^2$ = OMe, R3 = H | **10** | 69 (0) |
| 6 | **11**: $R^1$ = Me, $R^2$ = H, $R^3$ = OMe | **12** | 0 (–) |
| |  |  | |
| 7 | **13**: R = OMe | **14** | 66 (59) |
| 8 | **15**: R = Me | **16** | 86 (53) |
| |  |  | |
| 9[b] | **17**: R = H | **18** | 65 (99) |
| 10[b] | **19**: R = OMe | **20** | 77 (83) |
| |  |  | |
| 11 | **21** | **22** | 49 (79) |
| |  |  | |
| 12[b] | **23** | **24** | 71 (95) |
| |  |  | |
| 13 | **25** | **26** | 75 (87) |
| |  |  | |
| 14 | **27** | **26** | 47 (62) |

[a] Reactions were performed using $[Pd(MeCN)_4](BF_4)_2$ (5 mol %) and (*R*)-binap (10 mol %) in $(CH2Cl)_2$ at 60 °C for 6 h.
[b] Reaction temperature 50 °C, reaction time 24 h.




**Scheme 1.** Absolute configuration.

enantioselectivity at 50 °C (entry 9). Similarly, cyclohexenyl substituted enyne compounds gave the corresponding axially chiral biaryls in good yield with high enantioselectivity. With acyclic substituted enyne compounds, the geometry of the double bond affects significantly the reactivity and enantioselectivity as follows. E-Configurated enyne **25** gave axially chiral biaryl **26** in 75% yield with 86%ee (entry 13), while the corresponding *Z*-isomer **27** resulted in lower yield and enantioselectivity due to steric hindrance (entry 14). Both major enantiomers are of identical absolute configuration regardless of the geometry of starting material.

The absolute configuration of biaryl compound **18** obtained by the use of palladium/(*R*)-binap was determined as (*S*)-configuration by a comparison with the authentic compound (Scheme 1). Planar chiral enyne chromium complex (+)-**28**[14] was treated with $PPh_3AuNTf_2$ to give diastereoselectively *anti*-biaryl chromium complex[9] (+)-**29**. The stereochemistry of **29** was confirmed by X-ray crystallography.[15] A photo-oxidative demetallation of **29** afforded chromium-free axially chiral biaryl compound (+)-**18** which was identical with palladium-catalyzed cycloisomerization product **18** by chiral HPLC analysis.

In conclusion, the palladium-catalyzed asymmetric cycloisomerization of enynes with (*R*)-binap gave the axially chiral biaryls in good yields with moderate to good enantioselectivity.[16]

## Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.071.

## References and notes

1. For selected reviews: (a) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197–3210; (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427; (c) Kozlowsky, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207; (d) Bringmann, G.; Gulder, T.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563–639.
2. For recent selected references: (a) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 15798–15799; (b) Sawai, K.; Tatsumi, R.; Nakahodo, T.; Fujihara, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6917–6919; (c) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708–2710; (d) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278–11287; (e) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8844–8847; (g) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J. J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14*, 2258–2261; (h) Zhang, S.-S.; Wang, Z. Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5546–5549; (i) Genov, M.; Almorín, A.; Espinet, P. *Chem. Eur. J.* **2006**, *12*, 9346–9352; (j) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723–1724.
3. For selected references: (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153–8156; (b) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101–9102; (c) Cammidge, A. N.; Crépy, K. V. L. *Tetrahedron* **2004**, *60*, 4377–4386.
4. Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593–2595.
5. Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795–3797.
6. Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382–8383.
7. A review and selected references: (a) Tanaka, K. *Synlett* **2007**, 1977–1997; (b) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510–6512; (c) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737–4739; (d) Oppenheimer, J.; Johnson, W. L.; Figueroa, R.; Hayashi, R.; Hsung, R. P. *Tetrahedron* **2009**, *65*, 5001–5012; (e) Mori, F.; Fukawa, N.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2011**, *13*, 362–365.
8. (a) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264–6267; (b) Fürstner, A.; Kennedy, J. W. J. *Chem. Eur. J.* **2006**, *12*, 7398–7410; (c) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 411–414; (d) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809–5812; (e) Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340–9341.
9. (a) Michon, C.; Liu, S.; Hiragushi, S.; Uenishi, J.; Uemura, M. *Tetrahedron* **2008**, *64*, 11756–11762; (b) Michon, C.; Liu, S.; Hiragushi, S.; Uenishi, J.; Uemura, M. *Synlett* **2008**, 1321–1324.
10. Uemura, M. In *Org. React.*; Wiley: New Jersey, 2006; Vol. 67, p. 217.
11. For a selected review of metal-catalyzed cycloisomerization of enyne compounds: (a) Michelet, V.; Toullec, P. Y.; Genét, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315; Asymmetric version: (b) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048–1052; (c) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899–2929.
12. For selected examples of transition metal complex catalyzed asymmetric cycloisomerization of enyne compounds. Au(I) catalyst: (a) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633–4637; (b) Munoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300; (c) Chao, C.-M.; Vitale, M. R.; Toullec, P. Y.; Genét, J.-P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319–1323; Palladium catalyst: (d) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211–214; (e) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651–654; (f) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662–663; (g) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764–2765; (h) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704–4705; (i) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249–253; Rh catalyst: (j) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526–4529; (k) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3457–3460; (l) Lei, A.; Ne, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198–8199; (m) Chakrapani, H.; Liu, C.; Wiedenhoefer, R. A. *Org. Lett.* **2003**, *5*, 157–159; (n) Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2672–2676.
13. (a) Shibuya, T.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3963–3967; (b) Imase, H.; Suda, T.; Shibata, Y.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2009**, *11*, 1805–1808.
14. Planar chiral enyne chromium complex **28** was prepared from enantiomerically pure (+)-tricarbonyl(2-methoxy-6-methyl-1-bromobenzene)chromium by Sonogashira coupling with trimethylsilylacetylene followed by desilylation and further coupling with 1-cyclopentenyl-2-iodobenzene (see; Supplementary data).
15. Crysatallographic data of compound **29** (CCDC 895657).
16. Typical procedure of palladium-catalyzed asymmetric cycloisomerization; A mixture of $[Pd(MeCN)_4](BF_4)_2$ (2.30 mg, 5 mol %) and (*R*)-binap (6.90 mg, 10 mol %) in 1,2-dichloroethane (4 mL) was stirred at room temperature for 10 min under argon atmosphere. To the reaction mixture, a solution of 2-((2-cyclopentenylphenyl)ethynyl)-1-methoxy-3-methylbenzene (**17**) (30.4 mg, 0.105 mmol) in 1,2-dichloroethane (0.5 mL) was added by a syringe. The reaction mixture was heated at 50 °C for 24 h under argon, and cooled to room temperature. The mixture was diluted with ether and filtered through celite. The organic layer was evaporated under reduced pressure and the residue was purified by silica gel column chromatography with ether and hexane (1:20) to give 19.7 mg (65%) of 2-methoxy-6-methyl-1-{benzo((*b*)[2,3-dihydro-1*H*-inden-4-yl]benzene (**18**) as a colorless liquid; $[\alpha]_D^{20}$ + 5.4° (*c* 0.10, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (1H, d, *J* = 7.6 Hz), 7.82 (1H, d, *J* = 8.0 Hz), 7.47 (1H, t, *J* = 7.6 Hz), 7.48 (1H, s), 7.41 (1H, t, *J* = 7.6 Hz), 7.25 (1H, d, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 7.6 Hz), 6.84 (1H, d, *J* = 8.0 Hz), 3.69 (3H, s), 3.33 (2H, t, *J* = 7.6 Hz), 2.85–2.62 (2H, m), 2.24–2.16 (2H, m), 2.02 (3H, s); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 157.2, 141.6, 139.5, 137.9, 133.5, 133.1, 129.93, 129.92, 128.5, 128.1, 127.0, 125.6, 124.8, 124.5, 122.5, 108.3, 55.8, 32.9, 31.7, 24.4, 20.4; HRMS calcd for $C_{21}H_{20}O$: 288.1514. found 288.1520. HPLC (Chiralpak AD-H), UV detector 254 nm, 0.25% *i*-PrOH in hexane, flow rate 0.5 mL/min; retention time; 11.4 min (minor isomer), 15.7 min (major isomer).