ORGANIC LETTERS

2007
Vol. 9, No. 5
805−808

An Efficient One-Pot Asymmetric Synthesis of Biaryl Compounds via Diels–Alder/Retro-Diels–Alder Cascade Reactions

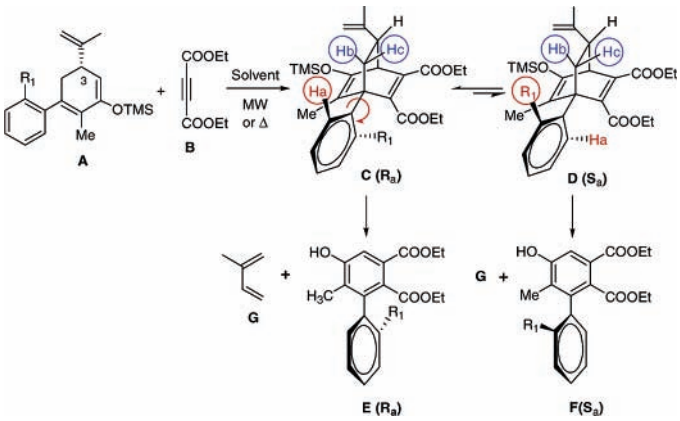
Yongxiang Liu, Kui Lu, Mingji Dai,[†] Kai Wang, Wanqing Wu, Jiahua Chen,* Junmin Quan,* and Zhen Yang*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry, Laboratory of Chemical Genomics, Shenzhen Graduate School, and the State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, Peking University, Beijing 100871, China

zyang@pku.edu.cn

Received December 13, 2006

ABSTRACT



A single-step chirality transfer method for the synthesis of axially chiral biaryl compounds by construction of the second aromatic ring via a Diels–Alder/retro-Diels–Alder cascade reaction is reported. This methodology should find broad application in the synthesis of natural products and asymmetric catalysts.

Axially chiral compounds are of great importance because of their decisive roles in governing the pharmacological properties of bioactive molecules[1] and controlling the catalytic outcomes in ligand-mediated asymmetric synthesis.[2]

Various synthetic methods have been exploited to make chiral biaryls,[3] which can be strategically divided into three categories: (a) resolution or desymmetrization of stereochemically undefined biaryls,[4] (b) direct atroposelective biaryl coupling,[5] and (c) atroposelective biaryl synthesis by construction of the second aromatic ring.[6]

[†] Current address: Department of Chemistry, Columbia University, New York, NY.

(1) (a) Nicolaou, K. C.; Boddy, C. N. C.; Bráse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. (b) Bringmann, G.; Menche, D.; Bezabih, M.; Abegaz, B. M.; Kaminsky, R. *Planta Med.* **1999**, *65*, 757. (c) Hubbard, B. K.; Walsh, C. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 730. (d) Kuroda, M.; Mimaki, Y.; Sakagami, H.; Sashida, Y. *J. Nat. Prod.* **2003**, *66*, 894. (e) Mutanyatta, J.; Bezabih, M.; Abegaz, B. M.; Dreyer, M.; Brun, R.; Kocher, N.; Bringmann, G. *Tetrahedron* **2005**, *61*, 8475.

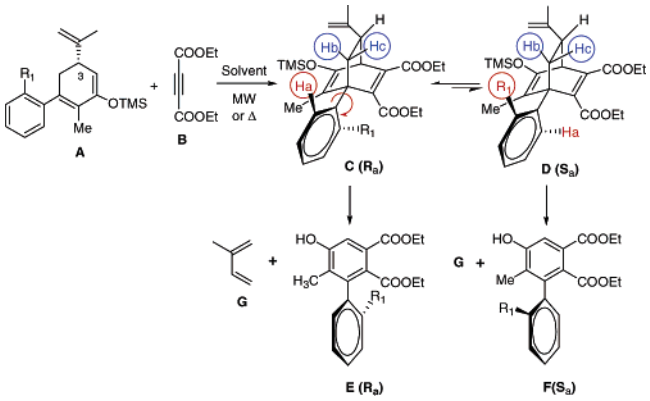
(2) (a) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; VCH: Weinheim, 2000. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (c) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809.

10.1021/ol063013b CCC: $37.00
Published on Web 02/01/2007

The third category has emerged recently and generally needs multiple steps to achieve chirality transfer. Recently, syntheses of biaryl skeleton-based natural products and ligands via Diels−Alder reaction have grown rapidly.[7] However, no asymmetric version has been reported so far. Herein, we wish to communicate *a single-step chirality transfer method for the synthesis of axially chiral biaryl compounds by construction of the second aromatic ring via Diels−Alder/retro-Diels−Alder cascade reactions*,[8] which should find broad application in the synthesis of natural products and asymmetric catalysts.

As shown in Scheme 1, the bicyclic intermediates **C** and **D** could be derived from cycloaddition of chiral diene **A**

Scheme 1. Formation of Axially Chiral Biaryl Molecules via the Diels−Alder/retro-Diels−Alder Cascade Reactions



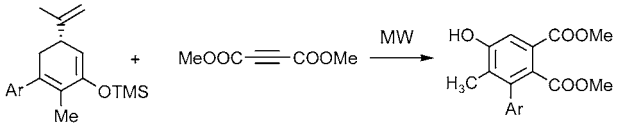
and dienophile **B**. With regard to the regiochemistry being controlled largely by the nature of electron-rich oxygenated diene[9] **A** and electron-deficient dienophile **B**, we envisioned that intermediate **C** would be formed predominately, in light of there being less steric interactions between **Ha** and **Hb**, **Hc** than those between $\mathbf{R_1}$ and **Hb**, **Hc** in intermediate **D**.

We also envisaged that, once formed, intermediate **C** would undergo a facile retro-Diels−Alder reaction, considering its congested nature, to give the axially chiral biaryl **E** and 2-methyl-1,3-butadiene **G**, realizing the chirality transfer from the chiral diene **A** to axial biaryl compound **E**. The key point in driving the conversion of **C**/**D** to **E**/**F** is the aromatization by fragmentation to give conjugated diene **G** instead of an alkyne (see later computational discussions).

It is worthwhile to mention that, in addition to the facile aromatization, the existing isopropenyl group at C3 of substrate **A** might provide an intrinsic instability in the bicyclic intermediate **C**, which would drive the retro-Diels−Alder reaction to the formation of **G**, rather than the reverse Diels−Alder reaction to starting materials **A** and **B**.

With the above in mind, we synthesized electron-rich dienes[9] **1a**−**i** from (*R*)-(−)-carvone (see the Supporting Information) and reacted them with dimethyl diacetylenedicarboxylate (DMAD) under microwave (MW) conditions to get the corresponding biaryl compounds listed in Table 1.

Table 1. Asymmetric Synthesis of Biaryl Compounds[a]



1a-1i **2a-2i**

entry	Ar	temp (°C)	time (min)	product	yield (%)[b]	ee (%)[c]
1	Me **1a**	140 80	5 60	**2a**	82 80	74 79 (91)[d]
2	Et **1b**	140 80	5 60	**2b**	83 78	72 77 (91)[d]
3	^{i}Pr **1c**	140 80	5 60	**2c**	70 61	72 78 (94)[d]
4	Cl **1d**	140 80	5 60	**2d**	70 65	73 76 (92)[d]
5	Br **1e**	140 80	5 60	**2e**	76 65	69 76 (91)[d]
6	CF_3 **1f**	140 80	5 60	**2f**	84 74	60 64 (90)[d]
7	OMe **1g**	140 80	5 60	**2g**	76 71	78 80 (96)[d]
8	Me, Br, Me **1h**	140 80	5 60	**2h**	60 56	64 72 (90)[d]
9	OMe **1i**	140 80	5 60	**2i**	65 60	16 71 (94)[d]

[a] Reagents and conditions: Reactions were run in a sealed tube with diene (1.0 mmol) and DMAD (2.0 mL) using a Biotage initiator microwave synthesizer under the conditions described in the Supporting Information. [b] Isolated yield. [c] Chiral HPLC. [d] Recrystallized yield in parentheses.

Accordingly, all reactions went to completion within 5 min under MW irradiation at 140 °C to give products **2a**-**2i** in a range of 65−84% yields with modest ee values (64−74%),

(3) For representative reviews, see: (a) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938. (b) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (c) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615. (d) Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223. (e) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.

(4) (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495. (b) Harada, T.; Tuyet, T. M. T.; Oku, A. *Org. Lett.* **2000**, *2*, 1319. (c) Ku, Y. Y.; Grieme, T.; Raje, P.; Sharma, P.; King, S. A.; Morton, H. E. *J. Am. Chem. Soc.* **2002**, *124*, 4282. (d) Bringmann, G.; Breuning, M.; Pfeifer, R.−M.; Schenk, W. A.; Kamikawa, K.; Uemura, M. *J. Organomet. Chem.* **2002**, *661*, 31. (e) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517.

(5) (a) Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3522. (b) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881. (c) Lipshutz, B. H.; Siegmann, K.; Garcia, E.; Kayser, F. *J. Am. Chem. Soc.* **1993**, *115*, 9276. (d) Uemura, M.; Kamikawa, K. *J. Chem. Soc. Chem. Commun.* **1994**, 2697. (e) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051. (f) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137. (g) Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron* **2004**, *60*, 4459.

except entry 9, in which only 16% ee was obtained. Prolonged reaction times did not improve the yields in all cases.

We then carried out the reactions at 80 °C, for 1 h, which gave relatively lower yields (56−80%) as compared with those obtained at 140 °C. However, the atroposelectivity improved (64−80% ee) at the lower temperature, especially in the case of entry 9, for which the ee value increased from 16% to 71%. We speculated that the lower atroposelectivity at the higher temperature might be caused by biaryl rotation.

In order to clarify the observation, product **2i** with 71% ee was heated at 140 °C for 10 min under MW irraditation; as expected, the ee value of **2i** dropped to ca. 3%, indicating that biaryl compound **2i**, with a methoxy group at its ortho position, easily rotated to cause the racemization.

To understand the outcome of enantioselectivity in the present cascade reactions, DFT calculations (B3LYP/6-31G)[10] were performed to elucidate the mechanistic details of reactions in entries 4 and 9 (Figure 1).

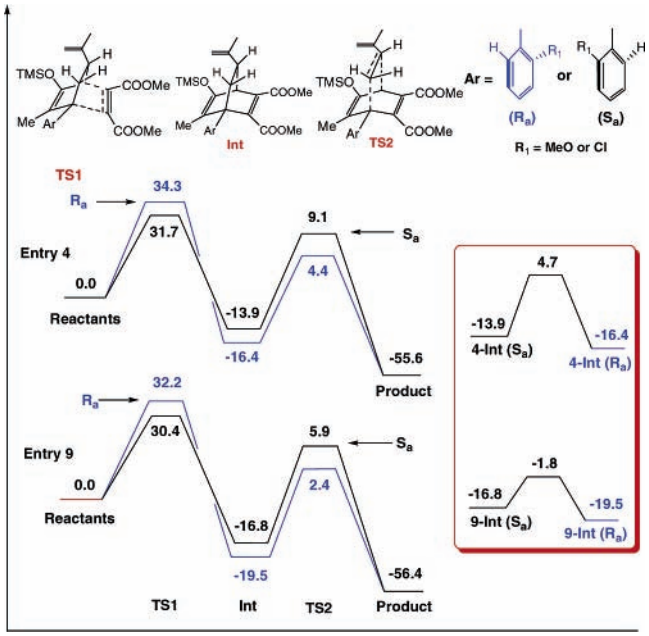


Figure 1. Mechanistic elucidation. The schematic free energy profile and the transition state structures and intermediates for the Diels−Alder/retro-Diels−Alder cascade reactions of entries 4 and 9. The inset is the transition barrier for the interconversion between the intermediates.

We speculated that each reaction in Figure 1 has two competitive pathways, labeled as R_a and S_a pathways, leading to formation of biaryls with R_a and S_a configurations, respectively. The computed free energy of activation for the Diels−Alder cycloaddition (**TS1**) is about 10 kcal/mol higher than **TS2** for the retro-Diels−Alder reaction which releases the 2-methyl-1,3-butadiene, indicating that the first step is rate-determining. Calculations indicate that, in both reactions of entries 4 and 9, **TS1** (R_a) is ca. 2 kcal/mol higher than **TS1** (S_a), suggesting that formation of intermediate with S_a configuration is favored in the first step. However, before going forward to the final product, the S_a configuration intermediate would shift to more stable R_a configuration due to relatively lower transition barrier. This is consistent with our early analysis. Therefore, formation of biaryls with R_a configuration is dominant. This preference of **TS1** (S_a) over **TS1** (R_a) is due to the steric repulsion between R_1 and the dienophile in **TS1** for the R_a pathway, as shown in Figure 2. The fact that **Int** (R_a) is more stable than **Int**(S_a) can be understood by the early analysis of Scheme 1.

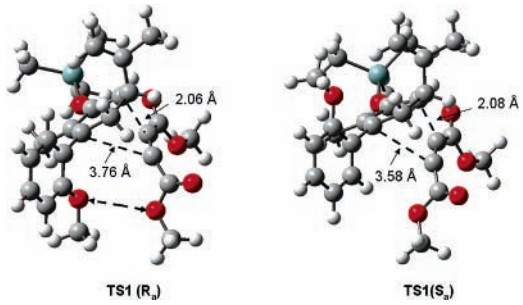


Figure 2. Computed transition-state structures of R_a and S_a pathways for the Diels−Alder cycloaddition step of entry 9 (distances in Å). The steric interaction between the substituent R_1 and the dienophile is indicated by the double arrows.

Rotation of biaryls leads to racemization, which would reduce enantioselectivity. Therefore, it is critical to know the rotation barrier for the products. For the small substituent, R_1 = MeO, the calculated barrier between R_a and S_a products is 32.8 kcal/mol, which is close to that of TS1; therefore, the rotation/racemization would occur at high temperature, as observed in our experiment. For the large substituent, R_1 = Cl, the calculated rotation barrier between R_a and S_a

(6) (a) Bao, J.; Wulff, W. D.; Fumo, M. J.; Grant, E. B.; Heller, D. P.; Whitcomb, M. C.; Yeung, S.-M. *J. Am. Chem. Soc.* **1996**, *118*, 2166. (b) Hattori, T.; Date, M.; Sakurai, K.; Morohashi, N.; Kosugi, H.; Miyano, S. *Tetrahedron Lett.* **2001**, *42*, 8035. (c) Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *J. Am. Chem. Soc.* **2002**, *124*, 6512. (d) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795. (e) Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358. (f) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382.

(7) (a) Reed, J. A.; Schilling, C. L.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188. (b) McDonald, E.; Suksamrarn, A.; Wylie, R. D. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1893. (c) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. (d) Sain, B.; Sandhu, J. S. *J. Org. Chem.* **1990**, *55*, 2545. (e) D'Auria, M. *Tetrahedron Lett.* **1995**, *36*, 6567. (f) Balázó, L.; Kádas, I.; Tõke, L. *Tetrahedron Lett.* **2000**, *41*, 7583. (g) Hilt, G.; Smolko, K. I. *Synthesis* **2002**, 686. (h) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908. (i) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737.

(8) (a) Alder, K.; Rickert, H. F. *Ann.* **1936**, *524*, 180. (b) Rubottom, G. M.; Krueger, D. S. *Tetrahedron Lett.* **1977**, *18*, 611. (c) Yang, Z.-Q.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602. (d) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881.

(9) (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381. (b) Danishefsky, S. *Tetrahedron* **1997**, *53*, 8689.

products is 39.4 kcal/mol, about 7 kcal/mol higher than **TS1**, so the final product is stable, even at 140 °C. Therefore, the substituent R_1 not only exerts its influence on the pathway for the Diels−Alder/retro-Diels−Alder cascade reactions, but also on the stability of the final product.

(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Revision B.05 ed. Gaussian, Inc: Pittsburgh, PA, 2003.

In conclusion, we have demonstrated a direct and atropoisomer-selective synthesis of axially chiral birayl compounds based on the MW-assisted Diels−Alder/retro-Diels−Alder reactions, and applied it to synthesize a series of biaryl compounds with good yields and moderate ee. Currently, we are working on growing crystals for X-ray studies of their absolute stereochemistry and on improving efficiency and the asymmetric induction of the reactions by evaluating the steric and electronic effects of substituents of our dienes.

Acknowledgment. This work is supported by grants from the National Science Foundation of China (20325208, 20225318, and 20521202).

Supporting Information Available: Experimental (including spectra) and calculation (including coordinates) details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063013B