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Rhodium-Catalyzed Asymmetric One-Pot Transesterification and [2 + 2 + 2] Cycloaddition Leading to Enantioenriched 3,3-Disubstituted Phthalides

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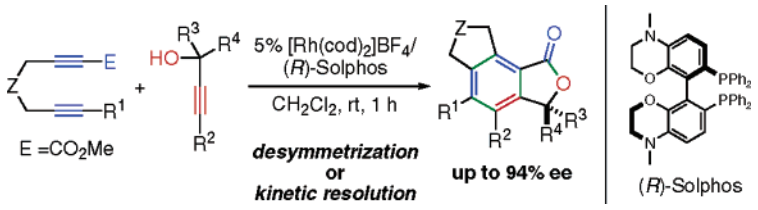
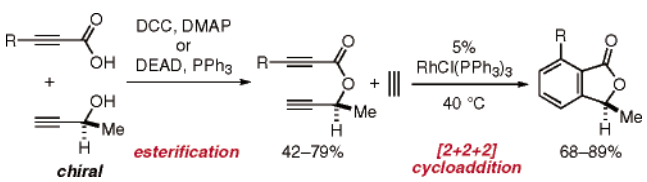
ABSTRACT



We have developed a cationic rhodium(I)/Solphos complex-catalyzed asymmetric one-pot transesterification and [2 + 2 + 2] cycloaddition of 1,6-diyne esters with tertiary propargylic alcohols leading to enantioenriched tricyclic 3,3-disubstituted phthalides. The present method represents a versatile new route to the synthesis of enantioenriched tricyclic 3,3-disubstituted phthalides in view of the easy access to both coupling partners.

Chiral 3-substituted phthalides occur in a number of biologycally active natural products,[1] so considerable effort has been paid to their *catalytic asymmetric* synthesis.[2] A transition-metal-catalyzed [2 + 2 + 2] cycloaddition[3] of chiral ester-linked diynes with monoalkynes is an attractive method because of the facile preparation of the former from propiolic acids and optically active propargylic alcohols.[4,5] Witulski and Zimmermann realized this process by using $RhCl(PPh_3)_3$ as a catalyst,[4] but this method is hard to apply to the synthesis of chiral 3,3-disubstituted phthalides due to difficulties of esterification and preparation of optically active tertiary propargylic alcohols (Scheme 1).

Scheme 1



Our research group first demonstrated that cationic rhodium(I)/modified-BINAP complexes are highly effective catalysts for chemo- and regioselective [2 + 2 + 2] cycloadditions.[6] These catalysts were further applied to the

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(1) Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984−2985 and refrences cited therein.
(2) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−631. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509−5512. (c) Everaere, K.; Scheffler, J.-L.; Mortreux, A.; Carpentier, J.-F. *Tetrahedron Lett.* **2001**, *42*, 1899−1901. (d) Lei, J.-G.; Hong, R.; Yuan, S.-G.; Lin, G.-Q. *Synlett* **2002**, 927−930.

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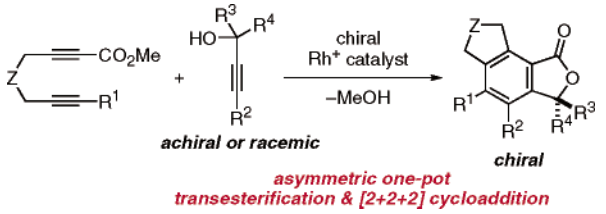
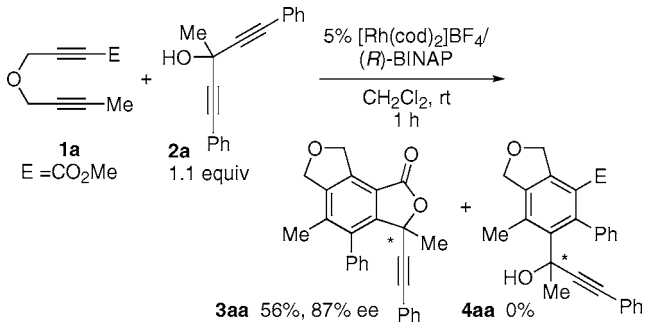
construction of axial,[7] planar,[8] and central[9] chiralities through enantioselective [2 + 2 + 2] cycloadditions. We anticipated that these complexes would catalyze the regio- and enantioselective formation of 3,3-disubstituted phthalides from diynes possessing an alkoxycarbonyl group at an alkyne terminus and tertiary propargylic alcohols through sequential one-pot transesterification and [2 + 2 + 2] cycloaddition due to the high Lewis acidity of a cationic rhodium (Scheme 2).[10,11] In this Letter, we describe a synthesis of enantioenriched tricyclic 3,3-disubstituted phthalides through a cationic rhodium(I)/Solphos[12] complex-catalyzed asymmetric one-pot transesterification and [2 + 2 + 2] cycloaddition.

Scheme 2



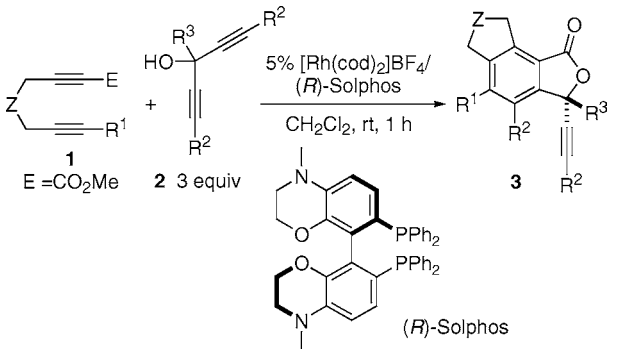
First the reaction of symmetrical bispropargylic alcohol **2a** and 1,6-diyne **1a** was examined in the presence of 5% $[Rh(cod)_2]BF_4$/(*R*)-BINAP at room temperature. We were pleased to find that desymmetrization of **2a** through the reaction with **1a** proceeded to give phthalide **3aa** in moderate yield with good ee without the formation of regioisomer **4aa** (Scheme 3).[13]

Scheme 3



After screening reaction conditions, the highest enantioselectivity was achieved by using (*R*)-Solphos ligand, and improved yield was achieved by increasing the amount of **2a** (3 equiv, 82% yield, 92% ee; Table 1, entry 1). Thus, we explored the scope of this process with respect to both 1,4-diynes and 1,6-diynes. Not only phenyl but methyl (**2b**, entry 2) and methoxymethyl (**2c**, entry 3) substituted 1,4-diynes reacted with **1a** to give the corresponding phthalides in high yields with high ee values. Desymmetrization of terminal

Table 1. $Rh(I)^+$/(*R*)-Solphos-Catalyzed Desymmetrization of Symmetrical Tertiary Bispropargylic Alcohols[a]



entry	**1** (Z, R^1)	**2** (R^2, R^3)	% yield (**3**)[b]	% ee
1	**1a** (O, Me)	**2a** (Ph, Me)	82 (**3aa**)	92
2	**1a** (O, Me)	**2b** (Me, Me)	67 (**3ab**)	90
3[c]	**1a** (O, Me)	**2c** (CH_2OMe, Me)	75 (**3ac**)	92
4	**1a** (O, Me)	**2d** (H, Me)	66 (**3ad**)	48
5[c,d]	**1a** (O, Me)	**2e** (Ph, Et)	66 (**3ae**)	87
6[d]	**1b** (NTs, Me)	**2a** (Ph, Me)	85 (**3ba**)	93
7[c,d]	**1b** (NTs, Me)	**2b** (Me, Me)	87 (**3bb**)	90 (*R*)
8[c]	**1c** (CH_2, CO_2Me)	**2a** (Ph, Me)	61 (**3ca**)	80
9[c–e]	**1c** (CH_2, CO_2Me)	**2f** (Me_3Si, Me)	53 (**3cf**)	79

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1** (0.20 mmol), **2** (0.60 mmol), and CH_2Cl_2 (2.0 mL) were employed. [b] Isolated yields based on **1**. [c] Diyne **1** was added dropwise over 10 min. [d] Reaction time: 3 h. [e] Ligand: (*R*)-BINAP.

(3) For recent reviews, see: (a) Chopade, P. R.; Louie, J. *Adv. Synth. Catal*. **2006**, *348*, 2307−2327. (b) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun*. **2006**, 2209−2217. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem*. **2005**, 4741−4767. (d) Yamamoto, Y. *Curr. Org. Chem*. **2005**, *9*, 503−519. (e) Fujiwara, M.; Ojima, I. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 7, pp 129−150. (f) Varela, J. A.; Saá, C. *Chem. Rev*. **2003**, *103*, 3787−3801. (g) Malacria, M.; Aubert, C.; Renaud J. L. In *Science of Synthesis*: *Houben-Weyl Methods for Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Georg Thieme Verlag: New York, 2001; Vol. 1, pp 439−530. (h) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, *100*, 2901−2915.

(4) (a) Witulski, B.; Zimmermann, A. *Synlett* **2002**, 1855−1859. (b) Application to the first total synthesis of alcyopterosin E, see ref 1.

(5) Ni, see: (a) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett*. **1999**, *40*, 5231−5234. (b) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed*. **2004**, *43*, 2436−2440. Ru, see: (c) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem*. **2004**, *2*, 1287−1294. $Rh(I)^+/H_8$-BINAP, see: (d) Tanaka, K.; Nishida. G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed*. **2004**, *43*, 6510−6512.

(6) Our first report on the cationic rhodium(I)/modified-BINAP-catalyzed inter- and intramolecular [2 + 2 + 2] cycloadditions, see: Tanaka, K.; Shirasaka, K. *Org. Lett*. **2003**, *5*, 4697−4699.

(7) (a) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett*. **2005**, *7*, 3119−3121. (b) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett*. **2005**, *7*, 4737−4739. (c) Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. *Org. Lett*. **2006**, *8*, 3489−3492. (d) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc*. **2006**, *128*, 4586−4587. (e) Tanaka, K.; Suda, T.; Noguchi, K.; Hirano, M. *J. Org. Chem*., published online Feb. 9, http://dx.doi.org/10.1021/jo0624546. (f) Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett*. **2007**, accepted for publication. (g) Also see ref 5d.

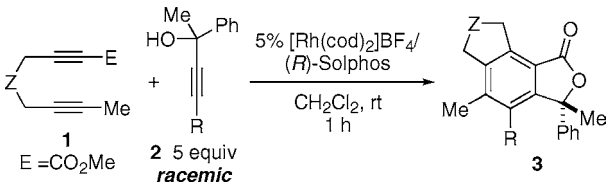
(8) (a) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem. Eur. J*. **2005**, *11*, 1145−1156. (b) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K. *Eur. J. Org. Chem*. **2006**, 3575−3581. (c) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc*. **2007**, *129*, 1522−1523.

(9) (a) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett*. **2006**, *8*, 907−909. (b) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem*. **2006**, 3917−3922.

1,4-diyne **2d** proceeded with moderate enantioselectivity despite a small difference in the steric demand between ethynyl and methyl (entry 4). Although slightly lower yield and ee were observed, 1,1-dialkynyl propanol **2e** could participate in this reaction (entry 5). With respect to 1,6-diynes, ether (**1a**, entries 1−5), tosylamide (**1b**, entries 6 and 7), and methylene (**1c**, entry 8) linked diynes could be employed. The reactions of sterically demanding trimethylsilyl-substituted 1,4-diyne **2f** with diyne monoesters **1a** and **1b** are inefficient, but **2f** reacted with diyne diester **1c** to give phthalide **3cf** in moderate yield with good ee by using (*R*)-BINAP as a ligand (entry 9).

The successful desymmetrization of symmetrical tertiary bispropargylic alcohols prompted our investigation into a kinetic resolution of racemic tertiary propargylic alcohols (Table 2). Although reactivities of them are lower than those

Table 2. $Rh(I)^+$/(*R*)-Solphos-Catalyzed Kinetic Resolution of Racemic Tertiary Propargylic Alcohols[a]



entry	**1** (Z)	**2** (R)	% yield (**3**)[b]	% ee
1	**1a** (O)	**2g** (Ph)	55 (**3ag**)	90
2	**1a** (O)	**2h** (Me)	56 (**3ah**)	94
3	**1b** (NTs)	**2g** (Ph)	79 (**3bg**)	86 (*R*)
4	**1b** (NTs)	**2h** (Me)	89 (**3bh**)	93

[a] $[Rh(cod)_2]BF_4$ (0.0075 mmol), ligand (0.0075 mmol), **1** (0.15 mmol), **2** (0.75 mmol), and CH_2Cl_2 (1.5 mL) were employed. Diyne **1** was added dropwise over 10 min. [b] Isolated yields based on **1**.

of tertiary bispropargylic alcohols, the reaction of racemic tertiary propargylic alcohols possessing phenyl (**2g**) or methyl (**2h**) at an alkyne terminus (5 equiv) with ether linked diyne **1a** proceeded to give the corresponding enantioenriched phthalides in moderate yields with high ee values (entries 1 and 2). The use of tosylamide linked diyne **1b** significantly improved the yields of phthalides (entries 3 and 4). The absolute configurations of both desymmetrization and kinetic resolution products, (+)-**3bb** and (+)-**3bg**, were determined to be *R* by the anomalous dispersion method (Figure 1).

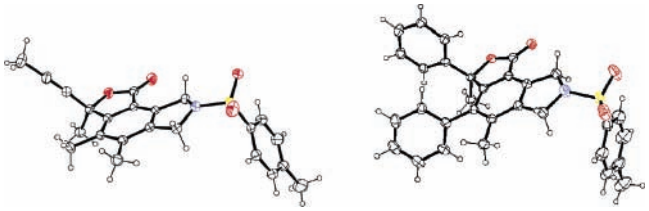
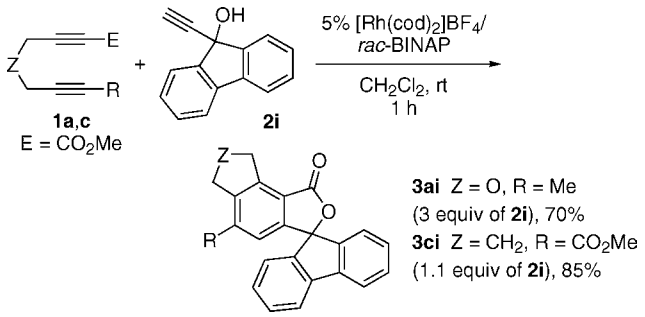


Figure 1. ORTEP drawing of (*R*)-(+)-**3bb** (left) and (*R*)-(+)-**3bg** (right).

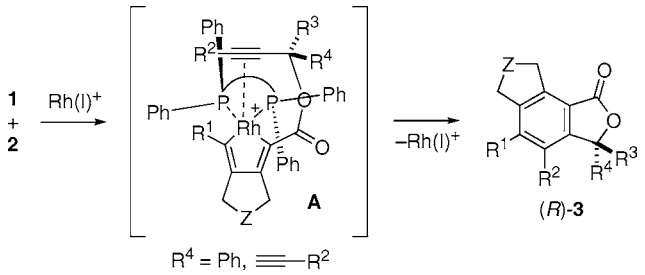
Scheme 4



The present sequential transesterification and [2 + 2 + 2] cycloaddition was applied to the synthesis of spiro phthalides, which are key structures of functional dyes such as thermal recording materials.[14] Commercially available 9-ethynyl-9*H*-fluoren-9-ol (**2i**) reacted with **1a** and **1c** to give spiro phthalides **3ai** and **3ci**, respectively, in high yields (Scheme 4).

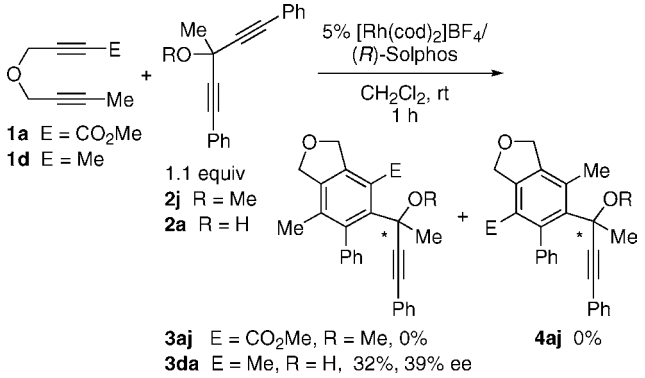
The observed high regio- and enantioselectivity can be explained by the selective formation of rhodium complex **A** through oxidative coupling of alkyne moieties of 1,6-diyne **1** and transesterification of the methoxycarbonyl group of **1**, activated by a cationic rhodium, with propargylic alcohol **2** (Scheme 5).

Scheme 5



Indeed, the use of propargylic ether **2j** did not furnish phthalides at all, and 1,6-diyne **1d** having no methoxycar-

Scheme 6



bonyl group reacted with **2a** to give cycloadduct **3da** with low ee (Scheme 6).

In conclusion, we have demonstrated that a cationic rhodium(I)/Solphos complex-catalyzed asymmetric one-pot transesterification and [2 + 2 + 2] cycloaddition represent a versatile new method for the synthesis of enantioenriched tricyclic 3,3-disubstituted phthalides in view of the easy access to both coupling partners.

Acknowledgment. We thank Solvias AG for the gift of (*R*)-Solphos under their University Ligand Kit program.

Supporting Information Available: Experimental procedures and compound characterization data, as well as X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL070179J

(10) For examples of transesterification in metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Takeuchi, R.; Nakaya, Y. *Org. Lett.* **2003**, *5*, 3659−3662. (b) Dieck, T. H.; Munz, C.; Müller, C. *J. Organomet. Chem*. **1990**, *384*, 243−255. (c) Abdulla, K.; Booth, B. L.; Stacey, C. *J. Organomet. Chem*. **1985**, *293*, 103−114.

(11) Ru-catalyzed sequential one-pot transesterification and [2 + 2 + 2] cycloaddition of alkynylboronates, see: (a) Yamamoto, Y.; Ishi, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc*. **2004**, *126*, 3712−3713. Its application to the synthesis of phthalides, see: (b) Yamamoto, Y.; Ishi, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc*. **2005**, *127*, 9625−9631.

(12) Pugin, B.; Martin, P.; Mueller, M.; Naud, F.; Spindler, F.; Thommen, M.; Melone, G.; Kesselgruber, M. WO 2004089920, 2004.

(13) For pioneering work on the desymmetrization of triynes through Ni-catalyzed [2 + 2 + 2] cycloadditions, see: Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133−6135.

(14) Selected recent examples, see: (a) Burkinshaw, S. M.; Griffiths, J.; Towns, A. D. *J. Mater. Chem*. **1998**, *8*, 2677−2683. (b) Pauze, R. H.; Waller, D. P.; Whritenour, D. C.; Zuraw, M. J. *J. Chem. Soc., Chem. Commun*. **1994**, 381−383.