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A Highly Enantioselective Allylic Amination Reaction Using a Commercially Available Chiral Rhodium Catalyst: Resolution of Racemic Allylic Carbonates

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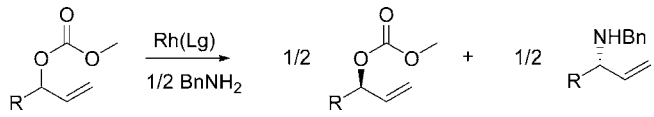
ABSTRACT



A novel method for the kinetic resolution of unsymmetrical acyclic allylic carbonates and the concurrent synthesis of enantioenriched secondary amines using a commercially available chiral catalyst is disclosed.

The stereochemical resolution of allylic carbonates and their analogous alcohols and the preparation of enantioenriched allylic amines are important because of the synthetic utility they provide in the construction of biologically important natural and unnatural products.[1,2] For the kinetic resolution of chiral racemic carbonates, the palladium-catalyzed allylic substitution has been the primary reaction.[3] Recently, other transition metals such as iridium and ruthenium have proven useful for this reaction.[4,5] Of the resolutions described, most are of cyclic or acyclic symmetric derivatives of allylic alcohols; there are few examples of the resolution of unsymmetrical acyclic allylic carbonates. Evans and coworkers have described the rhodium-catalyzed enantiospecific and regioselective allylic amination of enantiomerically enriched unsymmetrical allylic carbonates.[6] However, the rhodium-catalyzed enantioselective amination of allylic carbonates as well as the rhodium-catalyzed resolution of asymmetric acyclic allylic carbonates has not been described. Herein we describe a new method for the kinetic resolution of unsymmetrical acyclic allylic carbonates and the tandem regioselective synthesis of chiral secondary amines in high yield and enantioselectivity using a commercially available chiral rhodium catalyst.

During the course of our work, toward the synthesis of drug intermediates, we envisioned the rhodium-catalyzed

(1) For a recent review on allylic amination, see: Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(2) For the importance of resolved allyic carbonates and alcohols, see: (a) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int Ed.* **1998**, *37*, 1986. (d) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (e) Hanson, R. M. *Org. React.* **2002**, *60*, 1.

(3) For representative references of kinetic resolution in allylic substitutions using Pd catalysts, see: (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1090. (b) Gais, H.-J.; Eichelman, H.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Tetrahedron: Asymmetry.* **1998**, *9*, 235. (c) Ramdeehul, S.; Dierkes, P.; Aguado, R.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Osborn, J. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3118. (d) Reetz, M. T.; Sostmann, S. *J. Organomet. Chem.* **2000**, *603*, 105. (e) Longmire, J. M.; Wang, B.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 5435. (f) Gais, H.-J.; Spalthoff, N.; Jagusch, T.; Frank, M.; Raabe, G. *Tetrahedron Lett.* **2000**, *41*, 3809. (g) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237. (h) Lüssem, B. J.; Gais, H.-J. *J. Am. Chem. Soc.* **2003**, *125*, 6066. (i) Gais, H.-J.; Jagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem.—Eur. J.* **2003**, *9*, 4202. (j) Jansat, S.; Gómez, M.; Philippot, K.; Muller, G.; Guiu, E.; Claver, C.; Castillón, S.; Chaudret, B. *J. Am. Chem. Soc.* **2004**, *126*, 1592. (k) Faller, J. W.; Wilt, J. C.; Parr, J. *Org. Lett.* **2004**, *6*, 1301. (l) Lüssem, B. J.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041. (m) Gais, H.-J.; Bondarev, O.; Hetzer, R. *Tetrahedron Lett.* **2005**, *46*, 6279.

(4) Iridium as catalyst: Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(5) Ruthenium as catalyst: Onitsuka, K.; Matsushima, Y.; Takahashi, S. *Organometallics* **2005**, *24*, 6472.

(6) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

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resolution of unsymmetrical acyclic allylic carbonates as an intermediate process for the preparation of asymmetric allylic amines. To explore this hypothesis, we set up a screen in which racemic carbonate **1a** was reacted with 0.5 equiv of benzylamine in either methanol or tetrahydrofuran in the presence of nine different commercially available chiral rhodium catalysts frequently used for asymmetric hydrogenation.[7] Tetrahydrofuran was chosen for its wide use in the allylic substitution reaction, and methanol was chosen for its broad use in hydrogenations. A number of catalysts showed excellent activity (see the Supporting Information for a full list of catalysts and results). The three best catalysts for conversion and selectivity were (*S*)-Binapine-Rh (**4**), (*R*,*R*)-Ph-BPE-Rh (**5**), and (*S*,*S*,*R*,*R*)-Tangphos-Rh (**6**) (see Figure 1). All three catalysts are unprecedented for use in

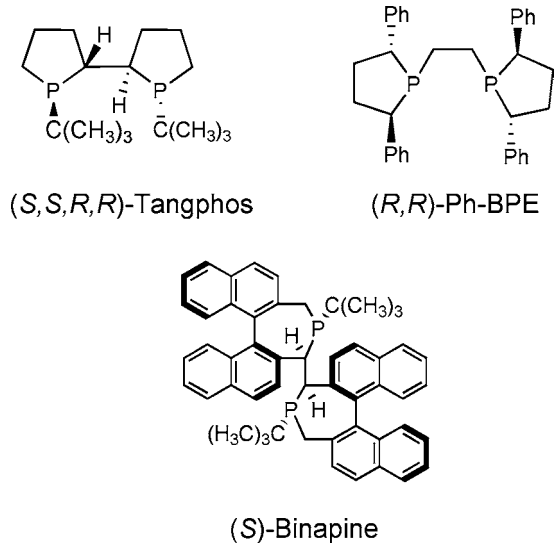


Figure 1. Ligand structures.

the allylic substitution reaction. These six reactions were repeated on a 1.0 mmol scale with a 1 mol % catalyst loading (Table 1). Our results show that (*S*)-Binapine-Rh and (*S*,*S*,*R*,*R*)-Tangphos-Rh are both excellent catalysts for the resolution of **1a**. In addition, the % ee's for the obtained secondary amine (**3a**) ranged from 89.0 to >99.9.

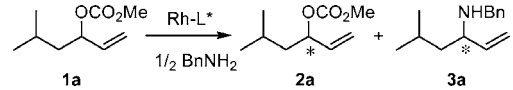
To demonstrate the generality of the reaction, carbonates **1a**−**e** were subjected to the resolution conditions using **6** as the catalyst on a 10.0 mmol scale to facilitate isolation and characterization of the products (Scheme 1, Table 2). The resolved carbonates **2a**−**d** were each a single enantiomer, and the amines **3a**−**d** were >91% ee.

(7) (a) Patent Pending, PCT/US02/35788 . (b) US Patent 5,021,131. (c) US Patent 5,171,892.

(8) (a) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (c) Evans, P. A., Leahy, D. K., In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 10, p 202.

(9) The reaction was run for 6 days to ensure completeness. HPLC assay of the crude reaction mixture showed no benzylamine present and **3a** integrated for 90%. The ratio of **3a** to its linear regioisomer was determined by ^{1}H NMR. The chiral assay of **3a** was 96.28% ee.

Table 1. Catalyst Screen for Resolution of **1a**

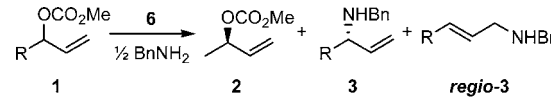


entry	ligand	solvent	yield of **3a**[b] (%)	ee **2a**[c] (%)	ee **3a**[c] (%)
1	(*S*)-binapine	MeOH	50	>99.9	>99.9
2	(*S*)-binapine	THF	10.2	9.5	>99.9
3	(*R*,*R*)-Ph-BPE	MeOH	39.0	66.3	97.6
4	(*R*,*R*)-Ph-BPE	THF	13.5	13.1	96.6
5	(*S*,*S*,*R*,*R*)-Tangphos	MeOH	35.2	45.7	89.0
6	(*S*,*S*,*R*,*R*)-Tangphos	THF	50	>99.9	97.3

[a] All reactions were carried out on a 1 mmol (**1a**) scale using 1 mol % of catalyst and 0.525 equiv of benzylamine at 0.5 M for 16 h. [b] Assay yield, theoretical yield is 50%, determined by the ratio of **3a** to benzylamine, no other UV-active products were formed in the reaction. [c] Limits of detection are ≤0.1%; see the Supporting Information for methods.

Carbonates **2a**−**d** were confirmed by optical rotation to have the *R* absolute configuration, while the amines **3a**−**d**

Scheme 1. Resolution of **1a**−**e** Using (*S*,*S*,*R*,*R*)-Tangphos-Rh



a: R = $(CH_3)_2CHCH_2$; **b**: R = Me; **c**: R = Et; **d**: R = $PhCH_2$; **e**: R = Ph

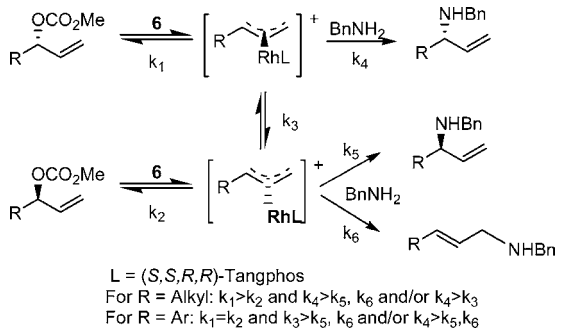
were confirmed by X-ray analysis to have the *S* absolute configuration (see the Supporting Information). Since **2a**−**d** and **3a**−**d** have opposite absolute stereochemistry, a double-inversion mechanism is implicated.[8] Presumably **6** is able to form matched/mismatched pairs with **1a**−**d** resulting in a rate difference between the conversion of (*S*)-**2a**−**d** and (*R*)-**2a**−**d** to (*S*)-**3a**−**d** and (*R*)-**3a**−**d**, respectively (Scheme 2).

Table 2. Preparation of **2a**−**d** and **3a**−**e** with (*S*,*S*,*R*,*R*)-Tangphos-Rh[a]

entry	**1**	yield[b] of **2** (%)	yield[b] **3** (%)	ee of **2**[c] (%)	ee of **3**[c] (%)	regio-**3**[d]
1	**1a**	44	34	>99.9	97.5	ND
2	**1b**	42	46	>99.9	95.2	ND
3	**1c**	47	49	>99.9	91.5	ND
4	**1d**	36	50	>99.9	>99.9	ND
5[e]	**1e**			16.1	89.0	ND
6[f]	**1e**		88		89.1	ND

[a] All reactions were carried out on a 10 mmol (**1**) scale using 0.005 equiv of (*S*,*S*,*R*,*R*)-Tangphos-Rh and 0.5 equiv of benzylamine in THF (0.5 M) for 3 h. [b] Isolated yield 50% is theoretical yield. [c] Limits of detection are ≤0.1%; see the Supporting Information for methods. [d] ND = not detected, determined by NMR, no resonances consistent with that expected for the regioisomers were observed. [e] Products were not isolated; the assay yield of **3** was 50%. [f] One equivalent of benzylamine used.

Scheme 2. Proposed Mechanism for the Kinetic Resolution of **1a**−**d** and the Asymmetric Transformation of **1e** to **3e**



The amines **3a**−**e** did not contain detectable amounts of the corresponding terminal regioisomers.

Interestingly, recovered carbonate **1e** showed very little resolution under the conditions, even though amine **3e** was 89.0% ee. Apparently, although **6** is able to form matched/mismatched pairs with **1a**−**d** its ability to do so with **1e** is greatly diminished. To capitalize on this phenomenon, we reacted **1e** with a full equivalent of benzylamine in the presence of **6**. As anticipated, **1e** was converted to **3e** in 88% isolated yield and 89.1% ee (entry 6). In order to determine if this outcome was unique to the benzylic carbonate, **1a** was reacted with a full equivalent of benzylamine to give complete conversion to a 55:45 mixture of **3a** to its linear regioisomer, respectively.[9]

In conclusion, we have discovered a novel method for the kinetic resolution of unsymmetrical acyclic allylic carbonates and the concurrent synthesis of enantioenriched secondary amines using a chiral rhodium catalyst. To the best of our knowledge, we are unaware of other examples of a rhodium-catalyzed enantioselective allylic amination or the resolution of acyclic asymmetric allylic carbonates. This resolution offers significant advantages over the current methodology: both the catalyst and nucleophile are commercially available and the product and unreacted starting material are easily separated by simple aqueous acidic extraction. The carbonates are isolated in >99.9% ee, and the amines are isolated in 91→ 99.9% ee free of linear regioisomers. The method is general for the aliphatic carbonates examined except benzylic carbonate **3e** which could be completely converted to its secondary amine in an enantio- and regioselective fashion.

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Supporting Information Available: General procedures for the catalyst screen, resolution of carbonates, and synthesis of amines; physical characterization data for resolved carbonates and amines, proof of absolute configuration of carbonates and amines including X-ray crystal structures for all amines, as well as analytical methods for determining the enantiomeric excess of all carbonates and amines. This material is available free of charge via the Internet at http://pubs.acs.org.

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