Enantiospecific Synthesis of Allylamines via the Regioselective Rhodium-Catalyzed Allylic Amination Reaction

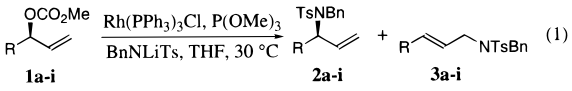
P. Andrew Evans,* John E. Robinson, and Jade D. Nelson

Brown Laboratory
Department of Chemistry and Biochemistry
University of Delaware
Newark, Delaware 19716

Received April 6, 1999

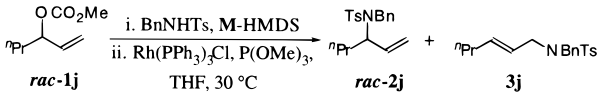
The transition metal-catalyzed allylic amination reaction provides a powerful method for the construction of chiral non-racemic allylamines that represent important building blocks for target-directed synthesis.[1] The allylic amination of cyclic and acyclic substrates, which proceeds through a symmetrical η^3-intermediate to circumvent potential regiochemical problems, furnish the requisite allylamine in high yield and with excellent enantioselectivity.[2] Racemic allylic epoxides also provide useful substrates for this type of transformation, affording amino alcohol derivatives with excellent regio- and enantioselectivity.[3] However, a recent survey of the metal-catalyzed allylic amination revealed a surprising paucity of methods that can facilitate the regio- and enantiospecific amination of *unsymmetrical* acyclic allylic alcohol derivatives.[1]

We recently demonstrated that Wilkinson's catalyst [$Rh(PPh_3)_3$-Cl] may be modified *in situ* with triorganophosphites to furnish a catalyst that facilitates the regioselective alkylation of acyclic unsymmetrical allylic carbonates.[4a] In the course of these investigations we established that the reaction proceeds with overall retention of absolute configuration *via* the proposed intermediacy of an *enyl* ($\sigma + \pi$) organorhodium intermediate.[4b,5] Herein, we describe the first regioselective rhodium-catalyzed allylic amination of a series of *unsymmetrical* acyclic enantiomerically enriched carbonates **1a**−**i** with the lithium anion of *N*-tosyl benzylamine to afford the secondary allylamines **2a**−**i** in high yield and with retention of absolute configuration (eq 1). These enantiomerically enriched intermediates represent useful synthons for the preparation of α-amino acids and nitrogen containing heterocycles (vide infra).



(1)

Table 1. Counter-Ion Effect on Regioselectivity in the Rh-Catalyzed Allylic Amination Reaction



entry	counterion **M**[a]	ratio **2j/3j**[b]	time (hrs)	yield (%)[c]
1	Li	3:1	1.5	84
2	Na	2.5:1	3.5	71
3	K	10:1	2.0	59

[a] All of the reactions were carried out on a 0.5 mmol reaction scale. [b] Ratios determined by capillary GLC. [c] Isolated yields.

Preliminary studies with classical nitrogen nucleophiles and the trimethyl phosphite *modified* Wilkinson's catalyst furnished the allylic amination products in poor yield, and with modest regioselectivity.[6] The ability to balance the nucleophilicity and basicity of the nucleophile was expected to moderate the reactivity of the nucleophile, and thus improve catalytic activity and reduce competitive elimination of the organometallic intermediate. The *N*-toluenesulfonyl benzylamine, prepared from benzylamine and *p*-toluenesulfonyl chloride, was anticipated to provide an improved nitrogen nucleophile. Hence, the effect of the counter-ion on solubility, turnover, and selectivity was examined. Treatment of the allylic carbonate ***rac*-1j** with the alkali metal-salt of *N*-toluenesulfonyl benzylamine and trimethyl phosphite *modified* Wilkinson's catalyst, furnished the corresponding allylic amination products ***rac*-2j/3j**, as outlined in Table 1. The nature of the counterion proved crucial, in which lithium was superior to both sodium and potassium, in terms of reaction rate and regioselectivity. The poor results obtained with sodium and potassium counterions were again attributed to low solubility and high basicity.

Table 2 summarizes the application of this transformation to a variety of enantiomerically enriched carbonates **1a**−**i**. *The excellent regioselectivities and reaction rates represent a unique solution to the metal-catalyzed allylic amination reaction.* The substituents examined indicate a high degree of tolerance in terms of the regioselective outcome. Interestingly, the degree of conservation of enantiomeric excess (cee)[7] from the carbonate to product appears to be independent of the regioselectivity (entries 3, 4, and 6). However, the enantiopurity of the allylic carbonates does influence the degree of cee in the amination product (entry 1).[8] The amination reaction proceeds with overall retention of absolute configuration,[9] which is consistent with a double

(1) For a recent review on allylic amination, see: Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689 and references therein. For a recent example of an enantioselective approach to allylamines, see: Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933.

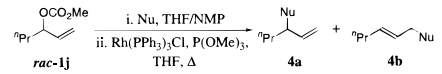
(2) For leading references on transition metal-catalyzed allylic amination reactions that proceed through symmetrical η^3-intermediates, see: (a) von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lefeber, C.; Feucht, T.; Helmchen, G. *Tetrahedron: Asymmetry* **1994**, *5*, 573. (b) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, T. *J. Am. Chem. Soc.* **1996**, *118*, 1031. (c) Burckhardt, U.; Baumann, M.; Trabesinger, G.; Gramlich, V,; Togni, A. *Organometallics* **1997**, *16*, 5252. (d) Trost, B. M.; Bunt, R. C *J. Am. Chem. Soc.* **1994**, *116*, 4089. (e) Trost, B. M.; Radinov, R. *J. Am. Chem. Soc.* **1997**, *119*, 5962 and references therein.

(3) For leading references to transition metal-catalyzed allylic amination using racemic vinyl epoxides, see: Trost, B. M.; Bunt, R. C. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 99.

(4) (a) Evans, P. A.; Nelson, J. D. *Tetrahedron Lett.* **1998**, *38*, 1725. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(5) Enyl complexes can be defined as those having a discrete σ- and π-metal carbon component within a single ligand. For definitions and examples, see: (a) Sharp P. R. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995, Chapter 2, p 272. (b) Lawson, D. N.; Osborn, J. A.; Wilkinson, G. *J. Chem. Soc. (A)* **1966**, 1733. (c) Tanaka, I.; Jin-no, N.; Kushida, T.; Tsutsui, N.; Ashida, T.; Suzuki, H.; Sakurai, H.; Moro-oka, Y.; Ikawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 657 and references therein.

(6) The poor results obtained with the hard nitrogen nucleophiles (Nu = PhthNK; **4a/b** = 2:1; TsNHLi; **4a/b** = 3:1), were attributed, at least in part, to their low solubility and high basicity which resulted in competitive elimination. Conversely, the softer nitrogen nucleophiles (Nu = $PhNH_2$; **4a/b** = 10:1; Ph_2NH.; **4a/b** = 1:9) provided homogeneous reaction mixtures that furnished the allylic amination adducts with improved regioselectivity. However, despite the improved selectivity the poor turnover rates and modest yields of **4a/b** deemed them unsuitable for preparative work, which was presumably due to competitive coordination of the nucleophile with the metal center. The crossover in regioselectivity for these nucleophiles is also rather interesting, and most likely a steric effect.



(7) The term conservation of enantiomeric excess {cee = (product ee/starting material ee) × 100} provides a convenient method of describing the enantiopecificity of the reaction

(8) The loss in enantiopurity for the conversion of **1a** to **2a** is not specific to this substrate, and was observed with other carbonates of similar enantiomeric purity (96% ee).

(9) The retention of absolute configuration in the rhodium-catalyzed amination, was assigned on the conversion of allylic carbonate **1e** to (*R*)-homophenylalanine, as outlined in Scheme 1.

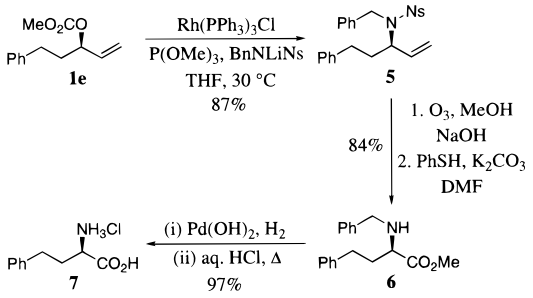
10.1021/ja991089f CCC: $18.00
Published on Web 07/02/1999

Table 2. Enantiospecific Rhodium-Catalyzed Allylic Amination of Chiral Non-Racemic Carbonates **1**[11]

entry	allylic carbonate **1**[a]		ee (%)[b]	ratio of **2/3**[c,d]	ee (%)[e]	cee[7] (%)	yield (%)[f]
1	Me	**a**	96	≥99:1	94	98	86
2	CH_2=$CH(CH_2)_3$	**b**	≥99	19:1	≥99	100	87
3	*c*Hex	**c**	≥99	9:1	≥99	100	92
4	$PhCH_2$	**d**	≥99	10:1	≥99	100	94
5	$PhCH_2CH_2$	**e**	≥99	20:1	≥99	100	89
6	$TBSOCH_2$	**f**	≥99	9:1	≥99	100	91
7	$BnOCH_2$	**g**	≥99	≥99:1	≥99	100	84
8	Ph	**h**	≥99	19:1	≥99	100	87
9	Npth	**i**	≥99	≥99:1	≥99	100	90

[a] All of the reactions were carried out on a 0.5 mmol reaction scale.[10] [b]Enantiomeric excess was determined on the parent alcohol or acetate derivative by chiral capillary GLC.[11] [c] Ratios of regioisomers were determined by HPLC on crude reaction mixtures. [d] The primary products were prepared independently via Pd(0) catalysis.[1] [e] Enantiomeric excess was determined by chiral HPLC. [f] Isolated yields.

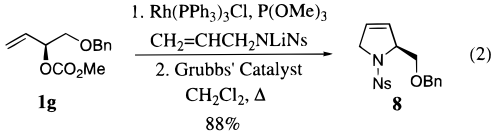
Scheme 1



inversion process proceeding through an *enyl* ($\sigma + \pi$)[5] organorhodium intermediate, analogous to the stabilized carbon nucleophiles.[4b]

The chiral nonracemic allylamine derivatives provide versatile synthons for target-directed synthesis, as outlined below. We anticipated that the forcing reaction conditions often employed for the removal of the *p*-toluenesulfonyl-protecting groups may prove problematic. Hence, the rhodium-catalyzed allylic amination was reexamined using the more labile *o*-nitrobenzenesulfonyl group, introduced by Fukuyama.[12] Scheme 1 outlines the application of this strategy to the preparation of (*R*)-homophenylalanine,[13−15] which is a component of a number of biologically active agents. The enantiospecific rhodium-catalyzed allylic amination of **1e** with the lithium anion of *N*-2-nitrobenzenesulfonyl benzylamine, furnished the allylamine **5** in 87% yield (≥99% ee), with significantly improved regioselectivity (2°:1° = 55:1; *cf.* Table 2, Entry 5). Ozonolysis of the alkene **5** in a sodium hydroxide/methanol solution afforded the methyl ester[16] which was treated with thiophenol to remove the 2-nitrobenzenesulfonyl group *via* the Meisenheimer complex,[12] to give the amino ester **6** in 84% overall yield. Hydrogenation of the hydrochloride salt of **6** followed by acid-catalyzed hydrolysis of the ester furnished (*R*)-homophenylalanine **7**[13] in 97% yield, identical in all respects to the reported data (^{1}H, ^{13}C and IR): $[\alpha]^{19}_D = -48$ (*c* = 1, 3 N HCl) [lit.[13] $[\alpha]^{21}_D = -46$ (*c* =1, 3 N HCl)].

The preparation of nitrogen-containing heterocycles remains both an important and challenging synthetic problem. Herein, we describe a two-step sequence for the preparation of enantiomerically enriched nitrogen-containing heterocycles. The rhodium-catalyzed allylic amination of **1g** with the lithium anion of *N*-*o*-nitrobenzenesulfonyl allylamine, furnished the corresponding allylamine in 92% yield, as a 33:1 mixture of regioisomers (≥99% ee). The diene was then subjected to ring-closing metathesis with 5 mol % of Grubbs' catalyst[17] to afford the pyrroline derivative **8** in 88% overall yield from **1g**.



(2)

In conclusion, we have developed a new method for the rhodium-catalyzed conversion of enantiomerically enriched *unsymmetrical* acyclic allylic carbonates to the corresponding differentially protected allylamines with excellent regioselectivity and conservation of enantiomeric excess. The *p*-toluenesulfonyl group was substituted for the more labile *o*-nitrobenzenesulfonyl derivative which improved the regioselectivity (2°:1°; Ts = 20:1 vs Ns = 55:1) with the allylic carbonate **1e**. The novel and highly regioselective rhodium-catalyzed allylic amination provides a convenient method for the construction of differentially protected chiral nonracemic allylamines, typically prepared from chiral pool intermediates through standard functional group manipulations, that provide versatile synthons for target-directed synthesis.

Acknowledgment. We sincerely thank the donors of the Petroleum Research Fund, administered by the American Chemical Society for generous financial support. We also thank Zeneca Pharmaceuticals for an Excellence in Research Award, Eli Lilly for a Young Faculty Grantee Award, Glaxo Wellcome for a Chemistry Scholar Award, and the Camille and Henry Dreyfus Foundation for a Camille Dreyfus Teacher-Scholar Award (P.A.E.).

Supporting Information Available: Spectral data for **1/2a**−**i**, ***rac*-1/2j** and **5**−**8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA991089F

(10) *Representative Experimental Procedure.* Trimethyl phosphite (24 μL, 0.20 mmol) was added directly to a red solution of Wilkinson's catalyst (47.3 mg, 0.051 mmol) in anhydrous THF (1.0 mL) at 30 °C, under an atmosphere of argon. The catalyst was allowed to form over *ca.* 30 min resulting in a light yellow homogeneous solution. Lithium hexamethyldisilylazide (1.0 mL, 1.0 mmol, 1.0 M solution in THF) was added dropwise to *p*-toluenesulfonyl benzylamine (0.262 g, 1.0 mmol) in anhydrous THF (3.0 mL) at 30 °C. The anion was allowed to form over ca. 30 min, added *via* Teflon cannula to the rhodium catalyst and rinsed with anhydrous THF (2 × 0.5 mL). The optically active allylic carbonate **1i** (120 mg, 0.5 mmol; ≥99% ee by capillary GLC analysis) was then added dropwise, *via* a tared 250 μL syringe, to the preformed rhodium catalyst. The mixture was heated at 30 °C for ca. 3 h (TLC control). The reaction mixture was partitioned between diethyl ether and, sequentially, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with a 5−15% ethyl acetate/hexane gradient) furnished the allylic amination product **2i** (0.193 g, 90%) as a straw-colored oil, with ≥99% ee by chiral HPLC analysis using a CHIRALCEL OD column.

(11) The enantiomerically enriched allylic alcohols were prepared using the Sharpless asymmetric kinetic resolution of the racemic allylic alcohol derivatives with dicyclohexyl tartrate; see: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(12) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(13) Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160.

(14) For a recent review on the asymmetric synthesis of α-amino acids, see: Davis, F. A.; Zhou, P.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13.

(15) For recent examples of asymmetric approaches to α-amino acids, see: (a) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445. (c) Drury, W. J., III.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (d) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284. (e) Tunge, J. A.; Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 4520 and references therein.

(16) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.

(17) For a recent review on ring-closing metathesis, see: Grubbs, R. H. *Tetrahedron* **1998**, *54*, 4413.