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Substituent effects on the amination of racemic allyl carbonates using commercially available chiral rhodium catalysts

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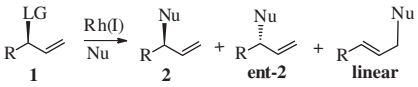
ABSTRACT

In the presence of commercially available chiral rhodium catalysts, a competitive benzylamination of racemic allyl carbonates, substituted with *p*-X-Ph groups, shows that the reaction proceeds faster with substituents (X) that are more electron-withdrawing. Mechanistic implications of these results are discussed.

Transition-metal-catalyzed asymmetric allylic substitution reactions continue to receive considerable attention with complexes of palladium,[1a–c] iridium,[1d] and rhodium[2] serving as important tools in synthesis. Madrahimov and Hartwig recently conducted mechanistic studies of iridium-catalyzed allylic substitution reactions that give products with overall retention of configuration as a result of two steps that occur with inversion of configuration.[1d] They concluded that factors controlling the enantioselectivity of these reactions are not the same as those of other metal ions such as palladium.

In the presence of Rh(I) catalysts, allylic substitution reactions often proceed with high regioselectivity.[3] Thus, substrates with secondary allylic leaving groups yield mostly branched substitution products whereas those with primary allylic leaving groups generate linear substitution products in high yields. A variety of compounds containing secondary allylic carbonates have been alkylated,[4] aminated,[5] and etherified[4h,6a,b] in excellent yields and high regioselectivities using rhodium catalysts. Allylic acetates have also been substituted with malonates using chiral[6c] and achiral[6d] rhodium catalysts.

The stereochemistry of rhodium-catalyzed allylic substitution reactions has also been examined. Chiral substrates **1** generally react with nucleophiles in the presence of an achiral catalyst to give branched products **2** with retention of stereochemical configuration in high yields



(1)

relative to enantiomer **ent-2** and linear structural isomers (Eq. 1).[4g–i,5a–d,6b,7] Interestingly, when Vrieze et al.[5d] reacted one equivalent of the racemic substrate rac-1 (R = CH_2Ph; LG = OCO_2CH_3) with one-half equivalent of $PhCH_2NH_2$ in the presence of the commercially available chiral rhodium catalyst, (*S*,*S*,*R*,*R*)-Tangphos-Rh (A in Fig. 1), they obtained a 36% yield (50% is theoretical) of unreacted **ent-1** in 99% ee and a 50% yield of **2** (R = CH_2Ph; Nu = $NHCH_2$ Ph) in 99% ee. These results demonstrate a kinetic resolution of **rac-1** in which **ent-1** reacts slower than **1** due to a 'mismatch' with

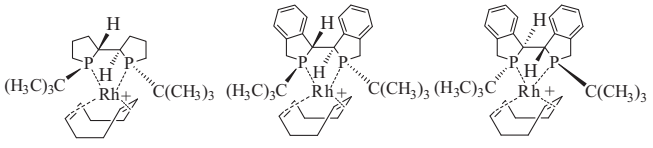


Figure 1. Rh(I) catalysts commercially available as BF_4^- salts.

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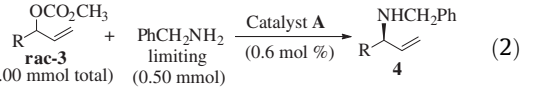
chiral catalyst **A**. On the other hand, **1** is 'matched' with **A** and reacts faster with $PhCH_2NH_2$ giving **2** almost quantitatively with retention of configuration.[5d]

Evans and co-workers have proposed a σ,π-coordinated (enyl)[8] or distorted π-allyl intermediate to account for the high regioselectivity and stereospecificity of rhodium-catalyzed allylic substitution reactions (Scheme 1).[4b,h] This mechanism explains the high yields of **2**, provided that the enyl intermediate undergoes a relatively slow π–σ–π rearrangement or metal–metal displacement. In this study, we aim to better understand this mechanism by determining substituent effects on the benzylamination of allyl carbonates using Rh(I) chiral catalysts.

Carbonates **rac-3** with electron-donating and electron-withdrawing substituents[9] were reacted competitively with benzylamine[10] in the presence of catalyst A (Eq. 2). [11] To a mixture containing 0.200 mmol of each of the five carbonates **rac-3a–e** (i.e., 1.00 mmol total) were added 0.500 mmol of benzylamine and a THF solution of **A** (Eq. 2). Given the 2:1 mole ratio of **rac-3** to benzylamine, the carbonates are forced to compete for benzylamine, the limiting reagent. The

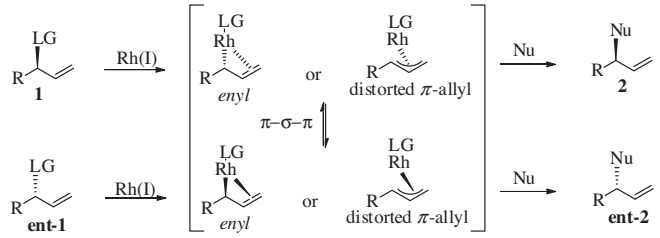
a; R = Ph
b; R = p-CH_3Ph
c; R = p-ClPh
d; R = p-CF_3Ph
e; R = p-NO_2Ph



(2)

extent of reaction was then determined from the crude reaction mixture using C-13 NMR. Although the integrals of carbon peaks are normally unreliable for making quantitative comparisons, the integrals of one of the vinyl carbons in carbonates **rac-3** are almost identical as shown in Figure 2a inset for an equimolar solution of the five carbonates before reaction. The NMR spectrum of the same vinyl carbon after reaction of an equimolar mixture of **rac-3** with one-half equivalent of benzylamine (Fig. 2b) shows the presence of both unreacted carbonates and product amines **4**. As expected, the peaks for **4** are at lower chemical shifts. It is clear from the integrations of these signals that the allylic substitution reaction goes faster as the substituents become more electron-withdrawing. Not surprising, the Hammett type plot in Figure 3 shows a good correlation between the negative logarithms of the unreacted carbonate integrals in Figure 2b and σ with $\rho = +0.36$. If the reaction rate depends upon the concentration of carbonate, which is likely, these integrals underestimate the relative reactivities of the carbonates because the more reactive a carbonate, the faster its concentration would decrease with time.

We next investigated the stereochemistry of the reaction of the five carbonates of **rac-3** separately with one-half equivalent of benzylamine in the presence of rhodium catalysts. In Table 1 are the % ee's of the recovered carbonates when catalyst **A** is used, which range in value from 42 to 49% and have the R absolute configuration based upon their optical rotations. Stereochemical data are also given in Table 1 for amines **4** formed in this reaction using



Scheme 1. Proposed mechanism for the transformation of **1** to **2** (and **ent-1** to **ent-2**) regioselectively and with retention of configuration.[4j]

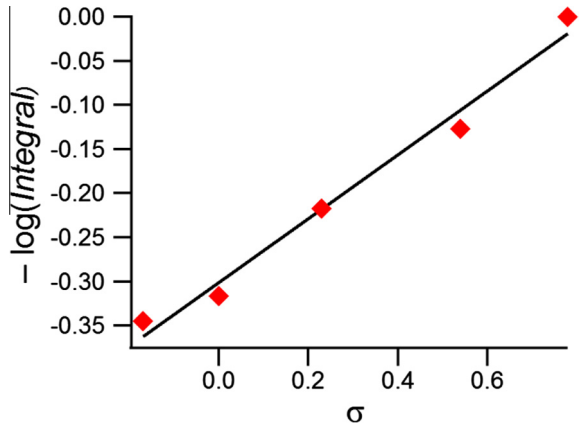


Figure 3. A Hammett type plot using the integrals of one of the vinyl carbons in the carbonate NMR spectra in Figure 2b. [−log (*integral*) = (0.36 ± 0.03)σ − (0.30 ± 0.01); $R^2 = 0.98$].

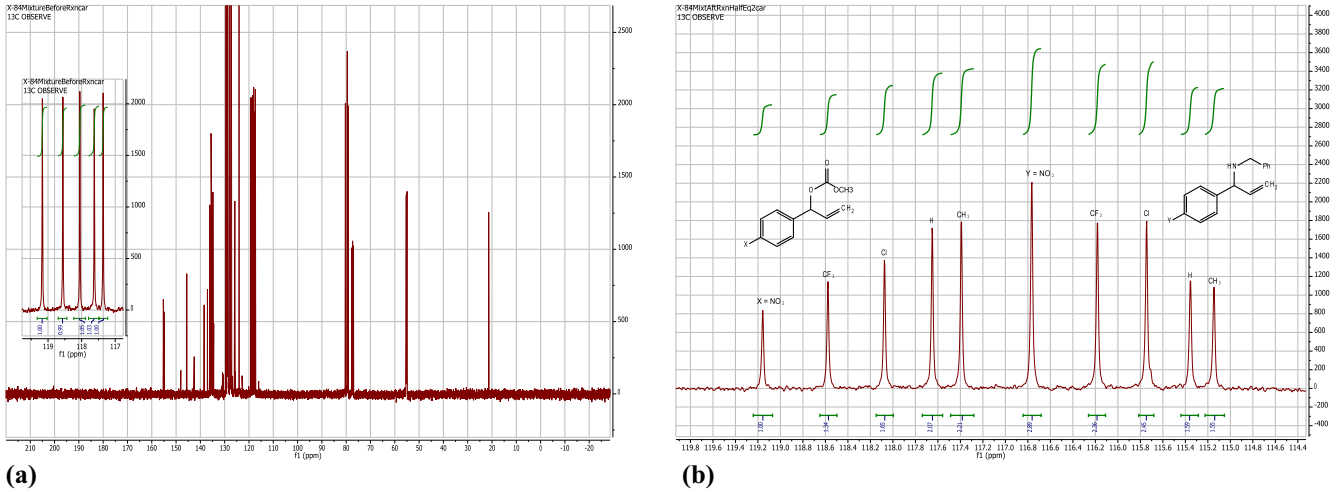
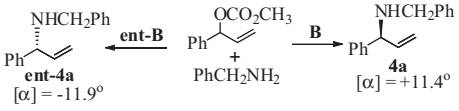


Figure 2. (a) C-13 NMR spectrum of an equimolar mixture of **rac-3a–e** with an inset of the region where one of the vinyl carbons in the five carbonates gives peaks. (b) Partial C-13 NMR spectrum of products from the reaction in Eq. 2 which is an expansion of the inset in (a) along with the peaks from the same carbon in amines **4** at slightly lower chemical shifts.

Table 1
Recovered carbonates and amines from the reaction of **rac-3** with one-half equivalent of $PhCH_2NH_2$ using rhodium catalysts[a]

Rac-3	Catalyst	% ee of Recovered carbonate[b]	Amine	% Yield of amine[c]	% ee of Amine[d]	[α]
a	**A**	49	**4a**	39	89[e]	
b	**A**	48	**4b**	43	—[f]	
c	**A**	44	**4c**	40	96	
d	**A**	48	**4d**	32	95[g]	
e	**A**	42	**4e**	41	—[f]	
a	**B**		**4a**			+11.4
b	**B**		**4b**			+8.4
c	**B**		**4c**			+7.0
d	**B**		**4d**			+8.8
e	**B**		**4e**			+16.8
a	**ent-B**		**ent-4a**			−11.9
b	**ent-B**		**ent-4b**			−8.9
c	**ent-B**		**ent-4c**			−7.8
d	**ent-B**		**ent-4d**			−9.8
e	**ent-B**		**ent-4e**			−17.7

[a] **ent-A** is not available commercially. Work in our laboratory and the Pfizer laboratory[5d] has shown that the two catalysts in Figure 1 give the same results within experimental error.
[b] From GC analysis of corresponding alcohols using a chiral column; major enantiomer has the *R* absolute configuration.
[c] Isolated yield of 50% is theoretical.
[d] Amines **4** have the *S* absolute configuration,[12] which was confirmed by X-ray analysis of the (*S*)-(+)-mandelic acid salts of **4b** and **4c**.
[e] Ref.[5d]
[f] Poorly resolved on chiral HPLC columns.
[g] From HPLC analysis of the Marfey derivatives of **4d** and **ent-4d**.



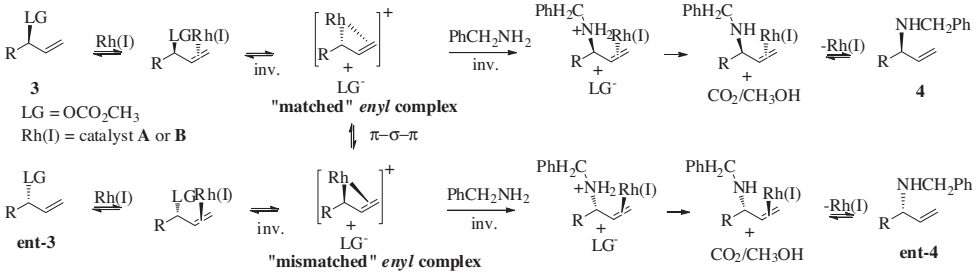
Scheme 2. Reaction of **rac-3a** with one-half equivalent of $PhCH_2NH_2$ using catalyst **B** and its enantiomer, **ent-B**.[12]

catalyst **A**. High % ee's are obtained from several of these amines, and crystal structures of **4a**,[5d] **4b**, and **4c** establish the *S* absolute configuration. Reaction of the five carbonates of **rac-3** separately with one-half equivalent of benzylamine was also carried out using catalyst **B** and its enantiomer, (*S,S,R,R*)-Duanphos-Rh (catalyst **ent-B**),[12] as shown in Scheme 2 for **rac-3a**. As expected, the specific rotation of +11.4° for **4a**[13] is almost identical to the +11.2° rotation that is obtained when this amine is made using catalyst **A**. The specific rotations of **4a–e** and **ent-4a–e** in Table 1 show that carbonates **rac-3a–e** react with one-half equivalent of benzylamine in the presence of these catalysts to generate amines with retention of configuration. The data in Table 1, along with the linear Hammett plot in Figure 3, are strong evidence that a common mechanism is operative in the competitive reaction in Eq. 2.

The observation that the reaction in Eq. 2 goes faster as the substituents become more electron-withdrawing gives more clarity to the mechanism in Scheme 1. The small, positive slope of +0.36 for ρ in the Hammett plot is consistent with a rate-determining step (RDS) which has a transition state that is electron rich relative to its reactant(s). It is reasonable to assume that the overall retention of configuration is the result of two inversions as has been previously shown for rhodium[4b]- and iridium-catalyzed allylic substitution reactions.[1d] A more detailed mechanism consistent with these observations is shown in Scheme 3.

The pathway for the conversion of carbonates **3** to amines **4** proceeds through a matched enyl complex with catalyst **A** or **B**, which makes this pathway faster than the one for the **ent-3** to **ent-4** conversion in which a mismatched complex forms. The high yield of **4** from the reaction of **rac-3** with one-half equivalent of benzylamine is the result then of a kinetic resolution which requires that the reaction of the matched enyl complex with benzylamine be faster than the rate of isomerization of the two enyl complexes via a π−σ−π process or metal–metal displacement.[4c] The matched enyl complex is presumably formed in two steps from **3**. Which step occurs first is open to speculation, but it seems unlikely that they would occur simultaneously. Given the small, positive ρ value of +0.36, either of the two inversion steps in the pathway from **3** to **4** could be rate-determining. Backside displacement at the benzylic carbon in **3** via an electron pair on Rh or N would be expected to increase the electron density in the transition step resulting in a positive ρ value. Theoretical work by Streitwieser et al., led them to conclude that electron-withdrawing groups lower the barriers of ionic S_N2 reactions.[14]

The mechanism in Scheme 3 also accounts for the relatively low ee's for the recovered carbonates in Table 1. If the reaction of the mismatched enyl complex with benzylamine is slow enough to make the π−σ−π rearrangement competitive, some **ent-3** would be converted to **3** resulting in a low ee for the carbonates in the



Scheme 3. Proposed mechanism for the reaction of **rac-3** with benzylamine using **A** or **B** as the Rh(I) catalyst.

reaction mixture. In fact, rearrangement of **ent-3c** to **3c** does occur under the conditions of the reaction in Eq. 2. When **rac-3c** was combined with catalyst **B** in the absence of benzylamine, the percentage of carbonate **3c**, the enantiomer with the *S* configuration, increased from 50 to 95. As expected, doing the same experiment with catalyst **ent-B**, resulted in a carbonate mixture with a high percentage of **ent-3c**, the carbonate enantiomer with the *R* configuration. Additional evidence of competition between the π−σ−π rearrangement of the mismatched enyl complex and its reaction with benzylamine comes from the reaction of one equivalent of **3a** with one equivalent of benzylamine using catalyst **A**, which gives **4** in 88% yield with an ee of 89%.[5d]

In conclusion, we have shown that the reaction of aryl-substituted allylic carbonates with benzylamine in the presence Rh(I) catalysts goes faster as the substituent in the aryl group becomes more electron-withdrawing. A mechanism in which a matched metal substrate complex (i.e., enyl complex) reacts with $PhCH_2NH_2$ is consistent with these results.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.032.

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9. *General procedure for preparing carbonates 3:*[19] To *p*-X-PhCH(CH=CH_2)OH containing 5–10% *p*-X-$PhCH_2OH$[1] (20.0 mmol) and pyridine (30.0 mmol) in 20 mL CH_2Cl_2 at ca. −10° was added methyl chloroformate (22.0 mmol) dropwise over 30–40 min. The mixture was allowed to warm slowly to room temperature. After ca. 24 h, the reaction mixture was transferred to a separatory funnel containing 50 mL ether and 20 mL sat NaCl. The aqueous layer was separated and washed with 25 mL ether. The ether layers were combined and dried over $CaCl_2$. The bulk of the ether was removed under reduced pressure in a rotary evaporator leaving a liquid that was chromatographed on silica gel and eluted with 4–5% ethyl acetate in hexanes (**3a–d**) or with 45:55 CH_2Cl_2–hexanes (**3e**). The desired carbonate was eluted first closely followed by the carbonate of the corresponding benzyl alcohol. Overall yields of *p*-X-PhCH(CH=CH_2)OCO_2CH_3 from *p*-X-PhCHO were in the range of 28–35%.
10. *General procedure for preparing amines 4:*[5d] In a glove box under nitrogen was combined 1.00 mmol **3**, 5 mol % of the catalyst, [Rh(1*S*,1*S*′,2*R*,2*R*′-tangphos)(COD)]BF_4, and 2 mL of deoxygenated THF. After stirring for several minutes, 54 mg of benzylamine (0.52 mmol) was added and the mixture was stirred for at least 16 h in the glove box. The reaction mixture was removed from the glove box and dissolved in 25 mL ether. The amine product **4** was extracted using 2.0 M HCl (3 × 20 mL). The aqueous extracts of the amine salt were combined, washed with ether (2 × 5 mL), and made basic with the addition of 7.0 mL of 2.5 M NaOH. The cloudy mixture containing **4** was extracted with ether (3 × 5 mL). The ether extracts were combined, washed, with sat. NaCl, and dried over $CaCl_2$. Removal of the ether under reduced pressure in a rotary evaporator left a viscous residue of **4** which could be purified by chromatography on silica gel and elution with 4–10% ethyl acetate in hexanes for **4a–d** and 2:3 CH_2Cl_2–hexanes for **4e**.
11. *Procedure for the competitive benzylamination of carbonates 3:* To a mixture of 0.20 mmol each of **3a**, **3b**, **3c**, **3d**, and **3e** in a glove box under nitrogen was added 2 mL of deoxygenated THF, 5 mol % of the catalyst, [Rh(1*S*,1*S*′,2*R*,2*R*′-tangphos)(COD)]BF_4, and 0.50 mmol of $PhCH_2NH_2$. After stirring overnight, the reaction mixture was removed from the glove box and the bulk of the THF was removed by evaporation. The residue was combined with 1 mL $CDCl_3$ and filtered to remove a small amount of solid, presumably, metal salts. The NMR spectrum in Figure 3 was recorded.
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17. *Procedure for derivatizing amine **4d** with Marfey's reagent (FDAA):*[19] A solution of 2.7 mg FDAA (1-fluoro-2-4-dinitrophenyl-5-L-alanine amide), 10 μL $(CH_3CH_2CH_2)_3N$, and 3.0 mg of **rac-4d** (or **4d**) in 100 mg DMSO was heated at 70° for 48 h. To the reaction mixture was added 40 μL of 2.0 M HCl followed by 8 mL ether. The water layer was separated and washed with 8 mL ether. The ether extracts were combined, washed with 6 mL water and 6 mL sat. NaCl, and dried over $CaCl_2$. After the ether was evaporated, the residue was dissolved in 45:55 heptane–IPA for HPLC analysis.
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