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Asymmetric Catalysis

Dynamic Kinetic Asymmetric Allylic Amination and Acyl Migration of Vinyl Aziridines with Imido Carboxylates**

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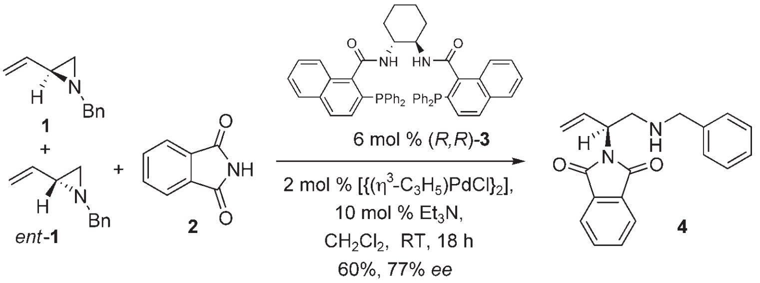
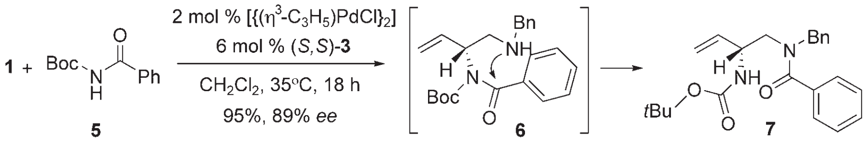
The palladium-catalyzed asymmetric allylic alkylation (AAA) has proven to be a versatile method for the preparation of synthetically useful materials.[1] Vinyl epoxides have shown a broad utility in related dynamic kinetic asymmetric transformations (DYKATs), wherein a racemic starting material is converted into an enantioenriched product.[2] Only recently has the cycloaddition of vinyl aziridines with isocyanates to afford chiral imidazolidinones been reported.[3] Although this methodology provides the valuable chiral vicinal diamine moiety[4] in high *ee*, its synthetic utility has been limited owing to the difficult differentiation of the resulting amines. In recent studies with imide nucleophiles, we discovered an atom-economical[5] DYKAT for the efficient preparation of useful orthogonally protected chiral vicinal diamines through use of imido carboxylates that undergo a facile in situ acyl migration. Application of the AAA enabled the formal synthesis of the potent PKC inhibitor balanol and its *cis* diastereomer.



(1)

By analogy to the DYKAT reactions with vinyl epoxides,[6] we first examined the asymmetric addition of phthalimide to the parent vinyl aziridine **1** with the use of diphosphine ligand **3** [Eq. (1)]. The addition of catalytic acetic acid, which was beneficial in the previous cycloadditions with isocyanates,[3] gave an increase in *ee* (47 to 82% *ee*) with a concomitant drop in yield (99 to 55%). The use of catalytic triethylamine instead provided a balance in improving the *ee* while affording a practical yield. A reasonable rationalization for the high enantioselectivity is the Curtin–Hammett kinetic amination of one diastereomeric η^3-allyl Pd^{II} complex from a pair which rapidly interconvert through a π–σ–π mechanism. Regioselectivity can be rationalized by an analogous hydrogen-bonding interaction between the H–N group of the imide nucleophile and the amine of the η^3-allyl Pd^{II} intermediate, as well as the directing effect of the ligand.[1]

When benzoyl imido carboxylates were examined as nucleophiles, a facile in situ acyl migration occurred, furnishing the protected N^1-benzoyl-N^2-*tert*-butoxycarbonyl vicinal diamine **7** in high enantioselectivity and yield [Eq. (2)]. The isomeric Boc acyl migration product was not observed, demonstrating the high selectivity for migration of the more electrophilic benzoyl group. Contrary to previous palladium-catalyzed DYKATs with vinyl aziridines,[3] the enantioselectivity was high without the use of an additive.



(2)

This dynamic kinetic asymmetric allylic amination and acyl migration proved general for a variety of benzoyl imido carboxylates to afford Boc-, Cbz-, ethoxycarbonyl-, and Troc-protected products (Table 1). Under current conditions, the reaction with acyl imido carboxylates affords only low yields. A similar highly enantioselective DYKAT and acyl migration was obtained with butadiene monoepoxide (Scheme 1). Saponification of ester **17** provided the known amino alcohol **18**[7] and established the absolute stereochemistry of the reaction. The products from the vinyl aziridine substrates were initially assigned by analogy. Subsequently, the absolute stereochemistry of the diamine products was confirmed by the synthesis of the azepane core of (+)-balanol (see below).

In an effort to furnish both amines protected with readily cleavable protecting groups, the use of imido dicarboxylates was examined. Similar to the previous reactions, the acyl

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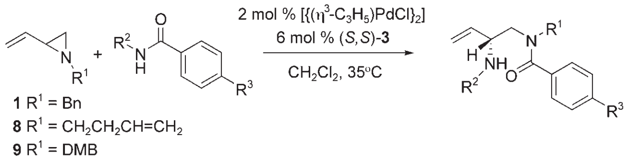
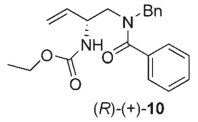
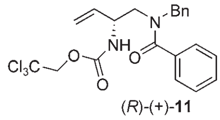
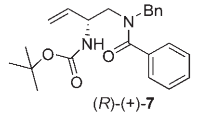
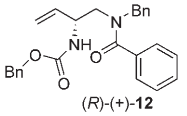
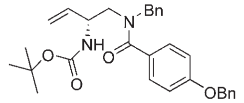
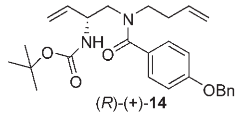
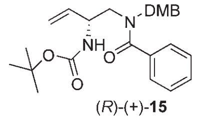
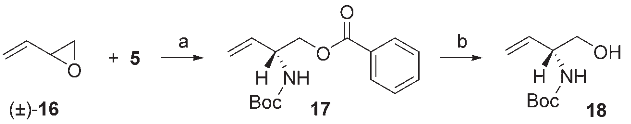
Table 1: Dynamic kinetic asymmetric allylic amination with benzoyl imido carboxylates.[a]



Entry	Aziridine	R^2	Product	ee[b] (yield)[c]
1	**1**	EtOCO	 (R)-(+)-**10**	89% (90%)
2	**1**	Troc	 (R)-(+)-**11**	93% (84%)
3	**1**	Boc	 (R)-(+)-**7**	89% (95%)
4	**1**	Cbz	 (R)-(+)-**12**	90% (75%)
5	**1**	Boc	 (R)-(+)-**13**	92% (81%)
6	**8**	Boc	 (R)-(+)-**14**	86% (97%)
7	**9**	Boc	 (R)-(+)-**15**	87% (90%)

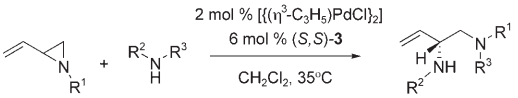
[a] Reaction conducted in dichloromethane (0.15 M) with 1.05 equiv imide. [b] Enantiomeric excess determined by chiral HPLC. [c] Yield of isolated product. Boc = *tert*-butoxycarbonyl. Bn = benzyl. Cbz = benzyloxycarbonyl. DMB = 2,4-dimethoxybenzyl. Troc = 2,2,2-trichloroethoxycarbonyl.

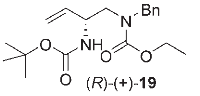
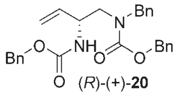
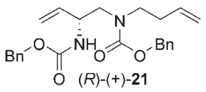
migration occurs through elimination of the carbamate functionality from a tetrahedral intermediate. However, the yields for this dynamic kinetic asymmetric allylic amination were slightly lower than with the analogous benzoyl imido carboxylates. This difference is likely a result of competitive fragmentations of the tetrahedral intermediate.[8] Generally, the AAA with ethyl, *tert*-butyl, and bisbenzyl imido dicarboxylates proceeded in high enantioselectivity and with reasonable yields. Entry 1 in Table 2 demonstrates that the chemoselectivity of the acyl migration is also controlled by steric factors. For example, with *tert*-butyl ethyl imido dicarboxylate, the ethyl carbamate functionality selectively migrated over the Boc.



Scheme 1. Dynamic kinetic asymmetric allylic alkylation with butadiene monoepoxide. a) 2 mol% [{(η³-C₃H₅)PdCl}₂], 6 mol% (S,S)-**3**, CH_2Cl_2, 35 °C, 18 h (72%, 90% *ee*). b) LiOH, H_2O, THF (86%).

Table 2: Dynamic kinetic asymmetric allylic amination with imido dicarboxylates.[a]

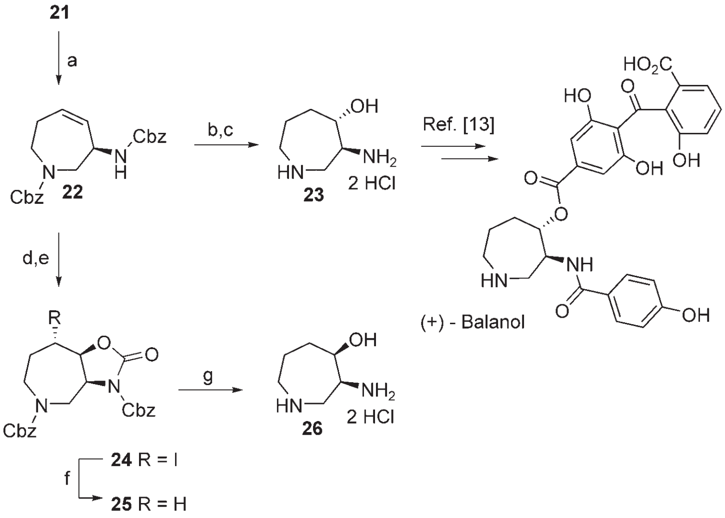


Entry	Aziridine	R^2, R^3	Product	ee[b] (Yield)[c]
1	**1**	Boc, EtOCO	 (R)-(+)-**19**	94% (71%)
2	**1**	Cbz, Cbz	 (R)-(+)-**20**	90% (67%)
3	**8**	Cbz, Cbz	 (R)-(+)-**21**	88% (68%)

[a] Reaction conducted in dichloromethane (0.15 M) with 1.05 equiv imide. [b] Enantiomeric excess determined by chiral HPLC. [c] Yield of isolated product.

To demonstrate the utility of the asymmetric amination, we turned our efforts towards the synthesis of the potent protein kinase C (PKC) inhibitor balanol (Scheme 2).[9] Ring-closing metathesis (RCM)[10] of the DYKAT product **21** provided the tetrahydroazepine intermediate **22**. Unlike other approaches towards balanol,[11] the stereochemistry at the hydroxy-bearing carbon was established from the olefin functionality created in the RCM. Our first approach relied on a regio- and diastereoselective hydroboration rationalized by the inductive and steric effects[12] resulting from the allylic carbamate. Optimal conditions furnished the azepane core in a 2:1 d.r. and 3:1 regioselectivity, from which the *anti* isomer was isolated in reasonable yield. Hydrogenolysis of the desired heterocycle completed the synthesis of the azepane intermediate **23** employed in the total synthesis of (+)-balanol reported by Lampe et al.[13]

Since the *syn* disubstituted azepane core[14] provides an alternative strategy to the *trans* stereochemistry of balanol as well as access to the *Z* analogues, which also are of interest, we evolved an efficient sequence to diastereomer **26**. After acylation of carbamate **22** with Boc anhydride, iodocyclization with NIS furnished oxazolidinone **24** in high yield. Dehalogenation with a tin-free protocol[15] and subsequent global deprotection completed the synthesis of the *syn* azepane **26** in quantitative yield, and in 77% overall yield from the metathesis product **21**. Performing the esterification of the hydroxy group with inversion of configuration will



Scheme 2. Formal synthesis of balanol and *epi*-C4-balanol. a) 5 mol% Grubbs II catalyst, CH_2Cl_2, 35 °C (90%), b) $BH_3 \cdot THF$, then $NaBO_3 \cdot H_2O$, 0 °C (47%), c) H_2, $Pd(OH)_2$, MeOH, then HCl (83%), d) $(Boc)_2O$, DMAP, CH_3CN, e) NIS, DCE, *hν* (79%, 2 steps), f) lauroyl peroxide, cyclohexane, *hν* (99%), g) HCl, H_2O, reflux (99%). DMAP = 4-dimethylaminopyridine, NIS = *N*-iodosuccinimide, DCE = dichloroethane.

allow this isomer to be converted into the natural diastereomer as well.

In conclusion, we have developed an efficient method for the preparation of chiral vicinal diamines and amino alcohols through a dynamic kinetic asymmetric allylic amination and acyl migration of vinyl aziridines and epoxides with imido carboxylates. The discovery of the facile acyl migration greatly expands the product scope and utility in natural product synthesis. Accordingly, the methodology provided a platform for the formal synthesis of balanol and analogues.

Experimental Section

Typical conditions for the dynamic kinetic asymmetric allylic amination of vinyl aziridines and epoxides with imido carboxylates: The catalyst solution was prepared by stirring under argon a mixture of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$ (2 mol% based on electrophile) and ligand (*S*,*S*)-**3** (6 mol% based on electrophile) in anhydrous and degassed dichloromethane (0.15 M based on electrophile) for 15 min at ambient temperature. The aziridine or epoxide was added to the catalyst solution by syringe, and the solution was transferred by cannula into an argon-purged vessel containing the nucleophile (1.05 equiv based on electrophile). The reaction mixture was stirred at 35 °C for 18 h, at which point the electrophile has been consumed by TLC. Concentration of the reaction mixture in vacuo gave an oil, and purification by silica gel chromatography (ether/hexanes) provided the desired product.

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[8] The lower yields of the desired products reported in Table 2 compared to those in Table 1 may result from the formation of a small amount of a by-product that may be the cyclic urea derived from loss of the alkoxy group in the tetrahedral intermediate of the isomerization step.

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