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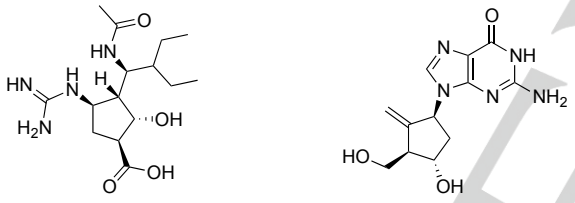
Stereocontrolled Synthesis of Amino-Substituted Carbocycles via Pd-Catalyzed Alkene Carboamination Reactions

Derick R. White and John P. Wolfe*

Abstract: Amino-substituted alkylidenecyclopentanes were synthesized through a stereoselective intermolecular Pd-catalyzed alkene carboamination reaction between alkenyl triflates bearing a pendant alkene and exogenous amine nucleophiles. The reactions are effective with a range of different substrate combinations, and proceed with generally high diastereoselectivity. Use of (*S*)-^{t}BuPhox as the ligand in reactions of achiral substrates provides enantioenriched products with up to 98.5:1.5 er.

The stereocontrolled synthesis of functionalized carbocycles bearing pendant amino groups is an important synthetic challenge due to the prevalence of these structures in biologically active compounds and pharmaceuticals.[1] For example, amino-substituted functionalized carbocycles peramavir (**1**)[2] and entecavir (**2**)[3] both display antiviral activities towards influenza and hepatitis B virus, respectively.



1 Peramavir
swine flu anti-viral

2 Entecavir
HBV anti-viral

Figure 1. Biologically active amino-substituted cyclopentane derivatives

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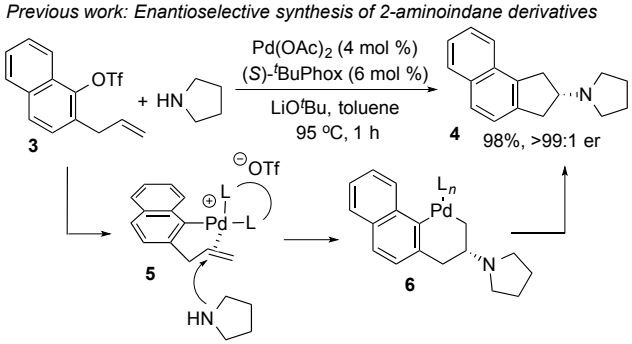
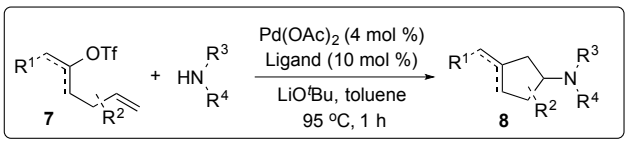
The stereocontrolled assembly of substituted aminocyclopentanes often requires multi-step sequences, such as conjugate addition to a cyclic α,β-unsaturated ketone followed by reductive amination and *N*-functionalization (alkylation, arylation, *etc.*); alkylative ring-opening of strained oxygen heterocycles or hetero-Diels-Alder adducts followed by subsequent Mitsunobu reaction, deprotection, and *N*-functionalization; or substitution reactions between carbocycles containing a 2°-leaving group and nitrogen nucleophiles.[1a,1c,1e,1f,2c,2d, 4 , 5 , 6] While these approaches do provide access to useful products, stereoselectivities are frequently modest, and separation of stereoisomers can be challenging.

We recently described a new asymmetric alkene carboamination reaction between substituted 2-allylphenyltriflate derivatives and exogenous amine nucleophiles that affords aminoindane derivatives (Scheme 1).[7,8] The transformations proceed via initial oxidative addition of the aryl triflate (e.g., **3**) to Pd(0), followed by complexation/activation of the proximal alkene to afford a cationic aryl Pd(II)-alkene complex **5**. This complex is captured by the amine nucleophile in an *anti*-aminopalladation reaction that affords **6**.[9] The 6-membered palladacycle **6** then undergoes reductive elimination to provide enantioenriched 2-aminoindanes (e.g., **4**) in excellent yield with up to >99:1 er.[7]

Previous work: Enantioselective synthesis of 2-aminoindane derivatives



This work: Stereoselective synthesis of alkylidenecyclopentylamines



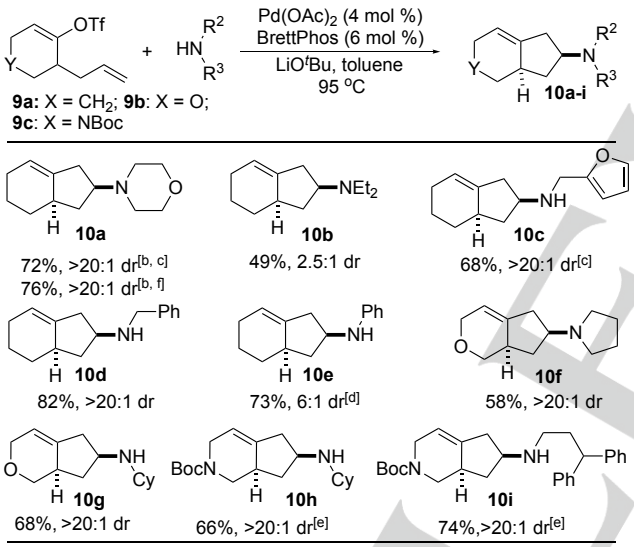
Scheme 1. Pd-catalyzed carboamination reactions for the synthesis of amino-substituted functionalized carbocycles

We reasoned a related strategy could be utilized for a concise, stereoselective synthesis of a variety of carbocycles by employing alkenyl triflate electrophiles.[10 - 11] As shown in Scheme 1, substrates such as **7** would be transformed to monocyclic or bicyclic alkylidenecyclopentanes **8** that contain

both amine and alkene functional groups that could potentially be further elaborated. In this Communication we describe our preliminary studies in this area, which provide access to a broad array of amino-substituted carbocycles in good yield with excellent stereocontrol.

The starting materials for these studies were readily synthesized from ketones, esters, or β-ketoesters in 2-5 steps via enolate allylation and subsequent enolate triflation.[12] In our initial studies we elected to examine the reactivity of cyclohexenyl triflates containing a pendant alkene (**9a**-**c**). Our previously reported conditions for the coupling of 2-allylphenyl triflates with amines proved effective for transformations involving alkenyl triflate substrates.[7] For example, treatment of 2-allylcyclohexen-1-yl triflate **9a** with morpholine in the presence of LiO^{t}Bu and a catalyst composed of $Pd(OAc)_2$ and BrettPhos afforded substituted bicyclo[4.3.0]nonene derivative **10a** in 72% yield with >20:1 dr (Table 1).[13] Similarly high yields and selectivities were observed with primary amine nucleophiles such as furfurylamine (**10c**), benzylamine (**10d**), cyclohexylamine (**10g**), and 3,3-diphenylpropylamine (**10i**).[14] The coupling of **9a** with morpholine provided comparable yields on both small (0.1 mmol) and large (1.0 g) scale.

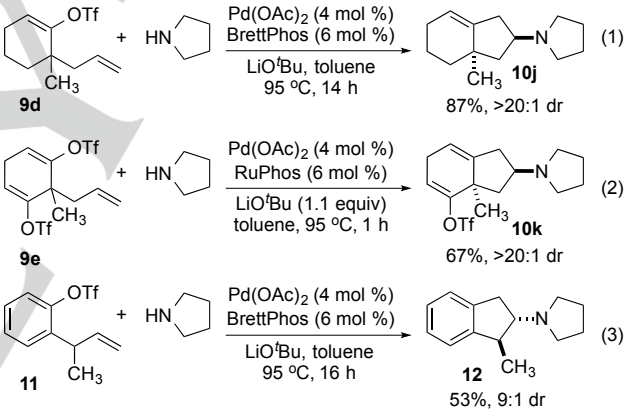
Table 1. Synthesis of amino-substituted bicycle[4.3.0]nonenes[a]



[a] Conditions: $Pd(OAc)_2$ (4 mol %), BrettPhos (6 mol %), alkenyl triflate (1 equiv), amine (1.2 equiv), LiO^{t}Bu (1.4 equiv), toluene [0.1M], 95 °C, 16 h. [b] The reaction was conducted at 70 °C. [c]10 mol % BrettPhos was used. [d]The reaction was conducted using 1 mol % $Pd_2(dba)_3$ and 4 mol % Phox as catalyst with no solvent. Crude dr = 4:1 by ^{1}H NMR analysis. [e]Diastereoselectivity was determined after cleavage of the Boc group. [f] The reaction was conducted on a 1 gram scale.

The nucleophilicity of the amine has a large impact on reactivity and stereocontrol, and use of amines that were either more hindered or less basic resulted in lower yields and selectivities. For example, the coupling of **9a** with diethylamine afforded **10b** in 49% yield and 2.5:1 dr, and attempts to couple **9a** with benzenesulfonamide or pyrrolidin-2-one failed to produce the desired product. Use of aniline as a nucleophile under standard conditions produced only trace amounts of **10e**. However, after extensive optimization we discovered the coupling of **9a** with aniline to afford **10e** proceeds in 73% yield and 6:1 dr when conducted without solvent using a catalyst composed of $Pd_2(dba)_3$ (1 mol %) and Phox (4 mol %).[15] The presence of heteroatoms on the substrate backbone was well tolerated, which provides access to amino substituted dihydropyrans **10f-g** or dihydropyridines **10h-i** in good yields and with excellent diastereoselectivities. Compounds **10f**-**g** are structurally related to the iridoid family of natural products, which are a large class of bicyclic monoterpenes that exhibit interesting biological activities.[16]

To further explore the scope of this method we examined the reactivity of substrates bearing a substituent on the tether between the alkenyl triflate and the alkene. A substrate bearing a methyl group at the homoallylic position (**9d**) was smoothly coupled with pyrrolidine to afford **10j** in 87% yield and >20:1 dr [Eq. (1)]. Similarly, bis-triflate substrate **9e** bearing a homoallylic methyl group was converted to substituted bicyclo[4.3.0]nonadiene product **10k**, which contains an unaffected passenger[17] alkenyl triflate that may be used for further synthetic manipulation, in 67% yield and >20:1 dr [Eq. (2)]. Aryl triflate substrate **11** bearing an allylic methyl group was transformed to *trans*-disubstituted aminoindane product **12** [Eq. (3)], albeit in slightly lower yield and selectivity (53%, 9:1 dr), which is likely due to the increased steric bulk near the alkene group.[18]

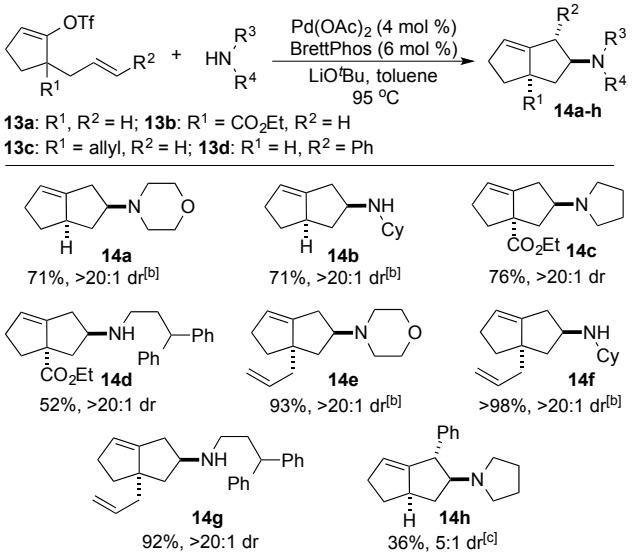


The Pd-catalyzed alkene carboamination reactions are also effective with cyclopentenyl triflate derivatives (**13a-d**). As shown in Table 2, the coupling reactions of these substrates with primary amines or cyclic secondary amines generally proceeded in good yield, and most products were obtained with high (>20:1) diastereoselectivity. Substitution at the homoallylic position was tolerated, as was the presence of an ester functional group (**14c-d)** or a second alkene (**14e-g**). Efforts to employ a substrate bearing a methyl group at the internal alkene carbon of the pendant allyl group were unsuccessful; the desired product was generated in low yield (<10%) along with a complex mixture of side products. However, use of substrate **13d** bearing an *E*-alkene afforded **14h** in modest 36% yield with 5:1 diastereoselectivity.[19]

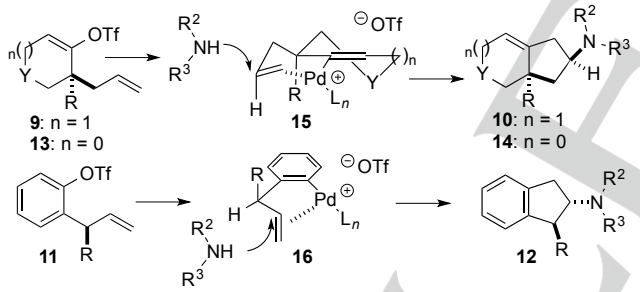
The high diastereoselectivities observed in reactions of **9**, **11**, and **13** are likely due to the highly organized nature of the transition state for alkene aminopalladation (Scheme 2). In the case of **9** and **13**, these transformations may proceed through

chair-like transition state **15** where the alkene is positioned to avoid a 1,3-diaxial interaction with the homoallylic R-group to afford **10** or **14**, respectively. The *trans*-disubstituted indane product **12** formed from **11** appears to be derived from transition state **16**, in which the allylic R-group is positioned *anti*-periplanar to the terminal methylene to avoid both allylic strain and eclipsing interactions with the incoming nucleophile.

Table 2. Synthesis of amino-substituted hexahydropentalenes[a]



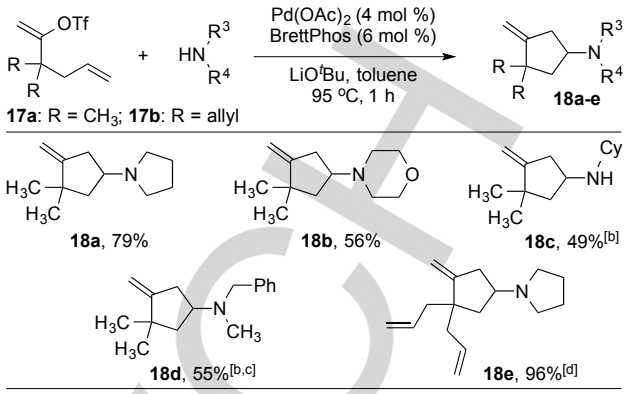
[a] Conditions: $Pd(OAc)_2$ (4 mol %), BrettPhos (6 mol %), alkenyl triflate (1 equiv), amine (1.2 equiv), LiO^{t}Bu (1.4 equiv), toluene [0.1M], 95 °C, 16 h. [b]10 mol % Brettphos was used. [c]The reaction was conducted using XPhos as ligand and 2 equiv pyrrolidine at [1M].



Scheme 2. Origin of diastereoselectivity in reactions of **9**, **11**, and **13**.

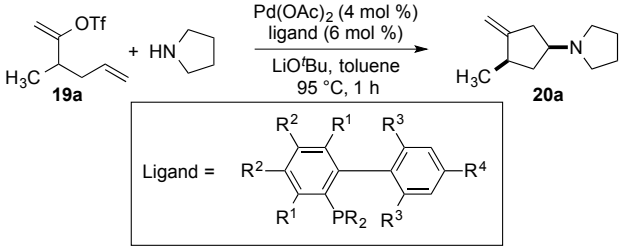
Having successfully developed conditions for transformations of cyclic alkenyl triflates, we elected to explore the reactivity of acyclic substrates. In our initial studies we prepared *gem*-disubstituted hexadienyl triflates **17a-b** and examined their coupling with various amines. We were pleased to discover these reactions afforded the desired monocyclic alkylidenecyclopentylamine products **18a-e** in moderate to excellent yields (Table 3). However, in some instances isomerization of the *exo*-alkene to afford substituted cyclopentene side products was problematic. After some experimentation we discovered the isomerization occurred only during prolonged reaction times, and could be alleviated by simply monitoring reactions such that heating was stopped and products were isolated as soon as the alkenyl triflate substrate had been completely consumed. The necessary reaction times were considerably shorter (<1.5 h) when stronger nucleophiles were used (*i.e.* pyrrolidine and morpholine); whereas, primary amines (**18c**) or acyclic secondary amines (**18d**) required longer reaction times (ca. 6 h).

Table 3. Synthesis of 3,3-disubstituted alkylidenecyclopentylamines[a]



[a] Conditions: $Pd(OAc)_2$ (4 mol %), BrettPhos (6 mol %), alkenyl triflate (1 equiv), amine (1.2 equiv), LiO^{t}Bu (1.4 equiv), toluene [0.1M], 95 °C, 1 h. [b]The reaction was conducted for 6 h . [c]The reaction was conducted using $P(C_6F_5)_3$ as ligand. [d] RuPhos was used as ligand and this product contained ca 5% of an inseparable unidentified impurity.

In order to explore diastereoselectivity in reactions of acyclic alkenyl triflates, we prepared 3-methyl-1,5-hexadien-2-yl triflate **19a** and examined its coupling with pyrrolidine. As shown in Scheme 3, use of our standard reaction conditions, in which Brettphos is employed as the ligand, afforded the desired product **20a** with only modest diastereoselectivity (3:1). In hopes of improving this selectivity we investigated the influence of ligand structure on stereocontrol, and discovered the nature of the ligand has a large impact on diastereoselectivity. Use of the very bulky Me_4^{t}Bu-XPhos ligand resulted in no stereocontrol (1:1 dr). However, ^{t}Bu-XPhos, which lacks substituents on the phosphine-bearing aryl ring, led to slightly improved results. Dicyclohexyl phosphine derivatives gave higher selectivity than di-*tert*-butyl phosphine derived ligands, and selectivity was further improved when ligands bearing more strongly electron donating groups on the second aromatic ring were employed. Finally, CPhos was identified as the optimal ligand, furnishing **20a** in 87% yield and 12:1 dr.[15]



Ligand Name	R	R^1	R^2	R^3	R^4	dr	yield
Me_4^{t}Bu-XPhos	^{t}Bu	Me	Me	^{i}Pr	^{i}Pr	1:1	80%
BrettPhos	Cy	OMe	H	^{i}Pr	^{i}Pr	3:1	49%[a]
^{t}Bu-XPhos	^{t}Bu	H	H	^{i}Pr	^{i}Pr	4:1	81%
RuPhos	Cy	H	H	O^{i}Pr	H	7:1	82%
CPhos	Cy	H	H	NMe_2	H	12:1	87%

[a] The reaction was conducted for 14 h.

Scheme 3. Influence of ligand structure on diastereoselectivity

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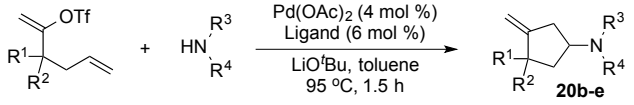
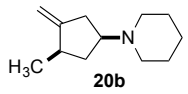
Having achieved acceptable levels of stereocontrol, we examined the coupling of **19a** and related dienyl triflates with various amine nucleophiles (Table 4). Although CPhos proved optimal in our initial experiments with **19a** and pyrrolidine, RuPhos proved superior to CPhos with other amine nucleophiles that were examined. As observed with cyclic triflates, the diastereoselectivities in these reactions were dependent on the nucleophile. For example, although reactions that employed pyrrolidine as a nucleophile afforded products with high diastereoselectivity (12:1 to >20:1 dr), use of piperidine (6:1 dr) or octylamine (4:1 dr) led to lower selectivities. Substrate **19c** bearing two substituents that differ substantially in size (methyl vs. phenyl) was transformed to product **20e** in 78% yield and >20:1 dr using RuPhos as ligand.

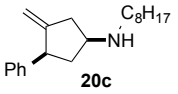
Table 4. Diastereoselective synthesis of substituted alkylidenecyclopentylamines



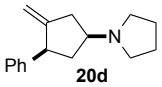
19a: $R^1 = CH_3$, $R^2 = H$; **19b**: $R^1 = Ph$, $R^2 = H$;
19c: $R^1 = Ph$, $R_2 = CH_3$



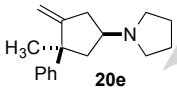
20b
91%, 6:1 dr (CPhos)
79% , 4:1 dr (RuPhos)



20c
70%, 4:1 dr (RuPhos)[b]



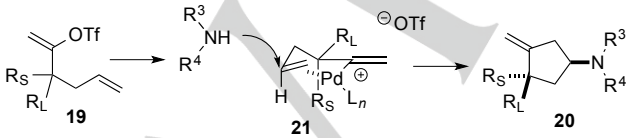
20d
98%, >20:1 dr (RuPhos)
65%, 3:1 dr (BrettPhos)



20e
78%, >20:1 dr (RuPhos)

[a] Conditions: $Pd(OAc)_2$ (4 mol %), Ligand (6 mol %), alkenyl triflate (1 equiv), amine (1.2 equiv), LiO^tBu (1.4 equiv), toluene [0.1M], 95 °C, 1.5 h. [b]The reaction was conducted for 6h .

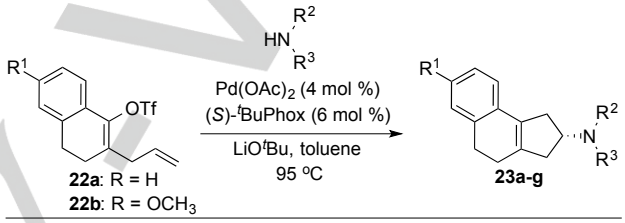
The stereoselectivity observed in reactions of acyclic substrates **19a-c** is likely due to similar factors that are in operation with cyclic alkenyl triflates. As shown in Scheme 4, these transformations may proceed through chair-like transition state **21**, in which the larger homoallylic substituent (R_L) is in a pseudoequatorial orientation to minimize 1,3-diaxial interactions with the alkenyl hydrogen atom. The observed product stereochemistry suggests the allylic strain between R_L and the Pd-bound alkene is less significant than the diaxial interactions, but may be responsible for the generally lower selectivities obtained with acyclic alkenyl triflates as compared to cyclic substrates.



Scheme 4. Origin of diastereoselectivity in reactions of **19**

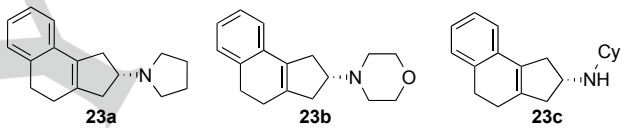
Finally, given our prior success in developing enantioselective reactions between substituted 2-allylphenyl triflate derivatives and amines, we briefly surveyed analogous asymmetric reactions of alkenyl triflates (Table 5). Our prior studies demonstrated that a catalyst composed of $Pd(OAc)_2$ and (*S*)-^{t}BuPhox provided high levels of asymmetric induction (Scheme 1).[7] Gratifyingly, this catalyst also proved to be effective with alkenyl triflate electrophiles **22a-b**. Use of 1°-amine nucleophiles such as cyclohexylamine and octylamine led to the generation of products with excellent stereocontrol (98.5:1.5 er), albeit in low yield (41% and 25% respectively). However, higher yields were obtained with more nucleophilic amines such as pyrrolidine or morpholine. In contrast, the bulkier and less nucleophilic *N*-benzylmethylamine produced **23g** in comparatively low selectivity (85:15 er) and moderate yield (50%). Efforts to induce asymmetric induction through coupling of **22a** with enantiomerically pure (99:1 er) (*S*)-α-methylbenzylamine were unsuccessful, as product **24** was generated in only 29% yield with very low (1.2:1) diastereoselectivity [Eq(4)]. However, both diastereomers were obtained in 99:1 er, which indicates the amine stereocenter does not epimerize before or after coupling.

Table 5. Enantioselective reactions of alkenyl triflates and various amines



22a: R = H
22b: R = OCH_3

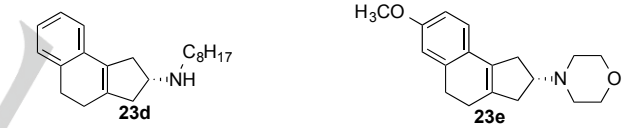
23a-g



23a
69%, 98:2 er

23b
75%, 94:6 er

23c
41%, 98.5:1.5 e.r.



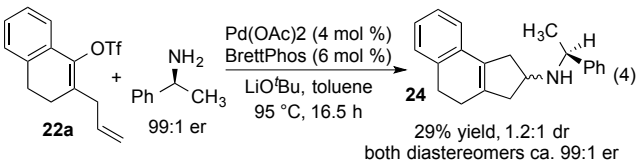
23d
25%, 98.5:1.5 er

23e
60%, 93:7 er

23f
60%, 98:2 er

23g
50%, 85:15 er

[a] Conditions: $Pd(OAc)_2$ (4 mol %), (*S*)-^{t}Bu-Phox (6 mol %), alkenyl triflate (1 equiv), amine (1.2 equiv), LiO^tBu (1.4 equiv), toluene [0.1M], 95 °C, 16 h.



29% yield, 1.2:1 dr
both diastereomers ca. 99:1 er

In conclusion, the Pd-catalyzed coupling of alkenyl triflates bearing pendant alkenes with amine nucleophiles provides a straightforward and stereoselective means of generating amino substituted alkylidenecyclopentane or cyclopentene derivatives. The transformations proceed via a key *anti*-aminopalladation reaction of a Pd(II)-alkene complex, which occurs through a

highly organized chair-like transition state. Use of the chiral (*S*)-^{t}BuPhox ligand in reactions of achiral substrates **22a-b** provides products with up to 98.5:1.5 er. Future studies will be directed towards further expanding the scope of these reactions to a broader array of nucleophiles, and to afford a variety of different carbocyclic systems.

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Keywords: stereoselective synthesis • asymmetric catalysis • enantioselective synthesis • carbocycle • palladium

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[19] The two stereoisomers appear to both have a *trans* relationship between the amino group and the phenyl group but are epimeric at the ring-fusion stereocenter.

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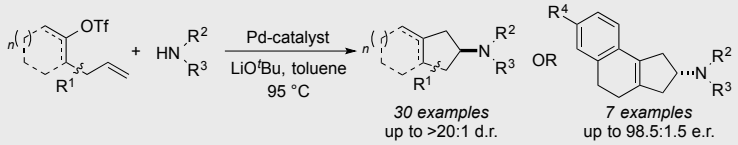

The Palladium-catalyzed coupling of amines with enol triflates derived from 2-allylcycloalkanones provides substituted alkylidenecyclopentylamine derivatives in good yield with high levels of stereoselectivity. Achiral substrates are transformed with up to 98.5:1.5 er.

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