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Desymmetrization of Bicyclo[3.*n*.1]-3-one Derivatives by Palladium-Catalyzed Asymmetric Allylic Alkylation

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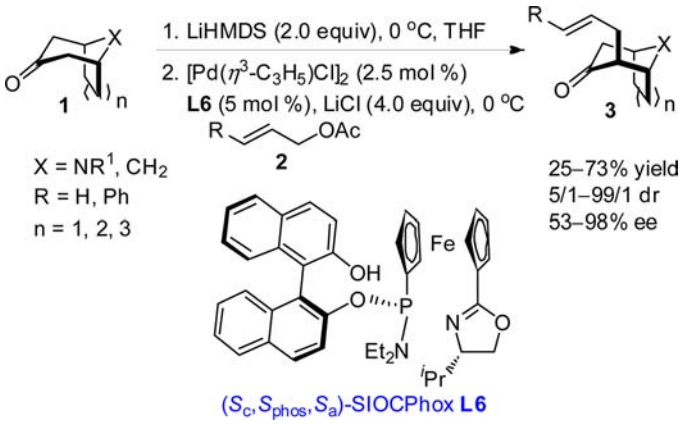
ABSTRACT



Desymmetrization of carbon nucleophiles by palladium-catalyzed asymmetric allylic alkylation has been realized for the first time. Products with three chiral centers were obtained in good yield and with high diastereo- and enantioselectivity. The method offers an efficient access to optically active tropane derivatives.

The tropane (8-azabicyclo[3.2.1]octane) ring system is present in a variety of valuable biologically active natural alkaloids such as atropine, scopolamine, and cocaine.[1] The synthesis of functionalized tropanes has attracted the attention of synthetic chemists due to their important role in accessing tropane alkaloids and their analogues.[2] Existing methods for the enantioselective synthesis of tropane derivatives rely heavily on the use of chiral building blocks, auxiliaries, and reagents.[2] The development of a catalytic asymmetric route would be highly desirable.

Enantioselective desymmetrization of a prochiral or *meso* substrate is a powerful synthetic tool for the synthesis of a range of optically active molecules.[3] Although many impressive advances have been realized, the reactions available for catalytic asymmetric desymmetrization are still limited. Palladium-catalyzed asymmetric allylic alkylations

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(AAA) have proven to be some of the most important methods for the asymmetric formation of C−C and C−X bonds.[4] These reactions have been demonstrated successfully in the desymmetrization of *meso*-allylic substrates.[5] In sharp contrast, examples of the desymmetrization of nucleophiles are very scarce and only isolated cases have been reported using *O*- or *N*-nucleophiles.[6] Recently, the desymmetrization of *meso*-carbon nucleophiles through dual palladium- and proline-catalyzed allylic alkylation was reported with moderate diastereoselectivity by Córdova and Breit respectively, but enantioselective control was not realized.[7] On the basis of our recent work on Pd-AAA using enolates as nucleophiles,[8] we envisioned that desymmetrization of 8-azabicyclo[3.2.1]-3-one by Pd-AAA might provide a possible method for the synthesis of optically active tropane derivatives bearing three chiral centers. In this communication, we disclose our preliminary results on this study.

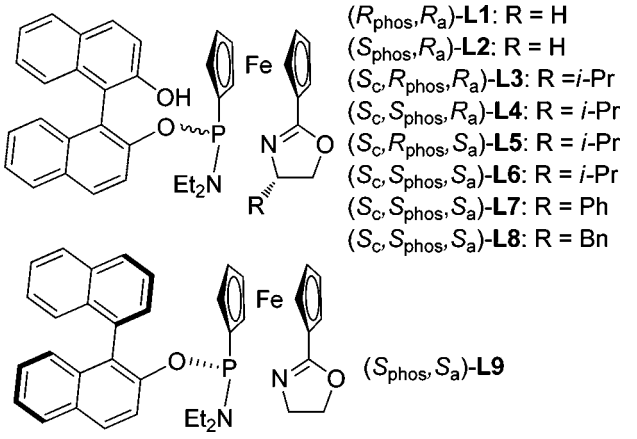
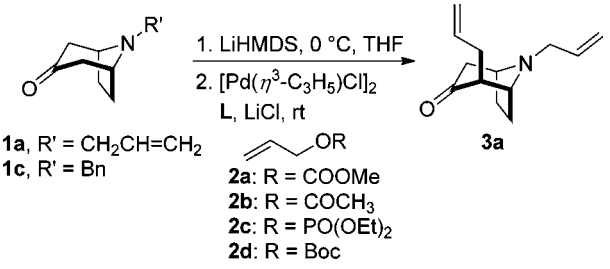


Figure 1. Ferrocene-based ligands SIOCPhox.

We commenced our studies using 8-allyl-nortropan-3-one (**1a**) as a model substrate. Initially, the nortropan-3-one **1a** was subjected to a reaction with allyl reagent **2a** under the effect of the catalyst derived from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and (R_{phos},R_a)-**L1** in the presence of LiHMDS (entry 1, Table 1). Allylation product **3a** was afforded in 43% yield and with 71% ee and excellent diastereoselectivity. Encouraged by these results, the impact of the chiral ferrocene-based SIOCPhox ligands on the reaction was investigated (Figure 1). Ligand (S_{phos},R_a)-**L2** gave much lower ee compared with (R_{phos},R_a)-**L1** (entry 2 vs 1, Table 1), which indicated that the chiralities in the ligand **L1** were matched. Further investigation of different combinations of chiral elements in the ferrocene-based ligands SIOCPhox uncovered that the chiralities in the ligand (S_c,S_{phos},S_a)-**L6** were matched (entries 3−6, Table 1). Then the influence of substituents on the oxazoline ring of SIOCPhox was examined (entries 6−8, Table 1) and the (S_c,S_{phos},S_a)-**L6** with isopropyl as the substituent proved to be the best ligand, affording the allylated product **3a** in 74% ee and in 44% yield. The use of (S_c,S_{phos},S_a)-**L7** led to a higher yield but an inferior enantiomeric ratio compared to (S_c,S_{phos},S_a)-**L6** (entry 6 vs 7, Table 1). With (S_c,S_{phos},S_a)-**L6** as the ligand, the allyl reagents **2** were evaluated (entries 9−11, Table 1). It was found that the acetate **2b** was superior in terms of the enantioselectivity (entry 9, Table 1). The yield decreased to 19% when the allyl **2c** was employed while 80% ee was obtained (entry 10, Table 1).

Table 1. Influence of Ligand and Allyl Substrates on the Pd-Catalyzed Desymmetrization of 8-Allyl-nortropan-3-one (**1a**)[a]



entry	**2**	ligand	yield (%)[b]	dr[c]	ee (%)[c]
1	**2a**	(R_{phos},R_a)-**L1**	43	99/1	67
2	**2a**	(S_{phos},R_a)-**L2**	41	99/1	32
3	**2a**	(S_c,R_{phos},R_a)-**L3**	43	99/1	32
4	**2a**	(S_c,S_{phos},R_a)-**L4**	36	63/1	7
5	**2a**	(S_c,R_{phos},S_a)-**L5**	48	>99/1	7
6	**2a**	(S_c,S_{phos},S_a)-**L6**	44	>99/1	74
7	**2a**	(S_c,S_{phos},S_a)-**L7**	66	>99/1	47
8	**2a**	(S_c,S_{phos},S_a)-**L8**	40	>99/1	47
9	**2b**	(S_c,S_{phos},S_a)-**L6**	43	99/1	81
10	**2c**	(S_c,S_{phos},S_a)-**L6**	19	99/1	80
11	**2d**	(S_c,S_{phos},S_a)-**L6**	45	49/1	64
12[d]	**2b**	(S_{phos},S_a)-**L9**	35	1/1.3	1/2

[a] Molar ratio of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/**L**/**1a**/**2**/LiHMDS/LiCl = 2.5/5/100/150/100/400. [b] Isolated yield. [c] Determined by chiral GC. [d] Compound **1c** was used as substrate.

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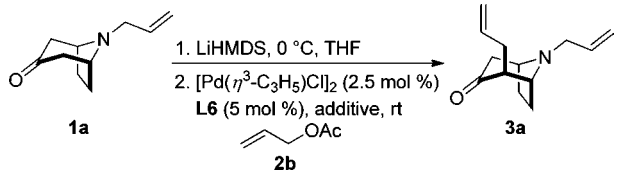
The ee value decreased to 64% in the case of the carbonate **2d** (entry 11, Table 1). The phenolic hydroxyl group of the SIOCPhox ligand was important to achieve high selectivity because a SIOCPhox **L9** bearing no −OH group gave both low diastereoselectivity and low enantioselectivity (entry 12, Table 1).

The additives played an important role in the Pd-catalyzed AAA using enolates as nucleophiles.[8a−d,9] Herein, we found some salts had dramatic effects on the yield and enantioselectivity of the reaction. The screening of additives revealed that both the lithium cation and chloride anion were crucial for the reaction. The absence of LiCl resulted in a sharp decrease in yield and enantioselectivity (entry 2 vs 1, Table 2). The use of other additives containing either a chloride anion or lithium cation gave inferior results compared with the use of LiCl (entries 3−6 vs 1, Table 2). We were delighted to observe the yield and enantioselectivity increased dramatically by raising the ratio of LiHMDS to the nortropan-3-one **1a** (entries 7−9, Table 2). Allylated product **3a** was produced in 68% yield and with 94% ee when 2 equiv of LiHMDS were used (entry 9, Table 2). We have no clear explanation for the phenomena at present. The presence of excess LiHMDS resulted in a decrease of diastereoselectivity (entry 8 vs 1, Table 2), which may be attributed to the epimerization of the product **3a**. Lowering the reaction temperature increased the diastereo- and enantioselectivity (entries 9 vs 8, Table 2). The results did not improve by using 3 equiv of LiHMDS (entry 10, Table 2).

The scope of the reaction was examined, and the results are compiled in Figure 2. A variety of 8-azabicyclo[3.*n*.1]-3-one gave the corresponding allylation products in good yield (**3a**−**3g**). Excellent diastereo- and enantioselectivities were also realized for *N*-methyltropinone, with the dr being 33:1, while the ee value was 91% (**3b**). The substituents on the nitrogen atom of the nortropan-3-one **1** affected the selectivity (**3c** and **3d**). Employing *N*-benzyltropinone as the substrate led to lower diastereo- and enantiomeric excesses (**3c**). Replacing the methyl group with a phenyl group in nortropan-3-one **1** gave a moderate diastereomeric excess, but the enantioselectivity remained excellent (**3d**). The reaction also occurred with excellent diastereo- and enantioselectivities for pseudopelletierine, with a 19:1 dr and 96% ee for product **3e**. 10-Methyl-10-aza-bicyclo-[4.3.1]decan-8-one was also a suitable substrate to give product (**3f**); however, the diastereomeric ratio was 1:1 in this case. Substituting *t*-BuOK for LiHMDS afforded the product **3f** with an improved diastereomeric ratio (15:1),

Table 2. Effect of Additive and Amount of LiHMDS on the Pd-Catalyzed Desymmetrization of 8-Allyl-nortropan-3-one (**1a**)[a]



entry	base (equiv)	additive	yield (%)[b]	dr[c]	ee (%)[c]
1	1	LiCl	43	99/1	81
2	1	–	27	>99/1	56
3	1	nBu$_4$NCl	37	99/1	46
4	1	ZnCl$_2$	30	32/1	15
5	1	LiClO$_4$	18	25/1	73
6	1	LiBr	9	26/1	46
7	1.2	LiCl	52	31/1	89
8	1.5	LiCl	60	20/1	89
9[d]	2	LiCl	68	32/1	94
10[d]	3	LiCl	65	28/1	93

[a] Molar ratio of [Pd(η^3-C$_3$H$_5$)Cl]$_2$/**L6**/**1a**/**2b**/LiHMDS/additive = 2.5/5/100/150/100−300/400. [b] Isolated yield. [c] Determined by chiral GC. [d] Reaction run at 0 °C.

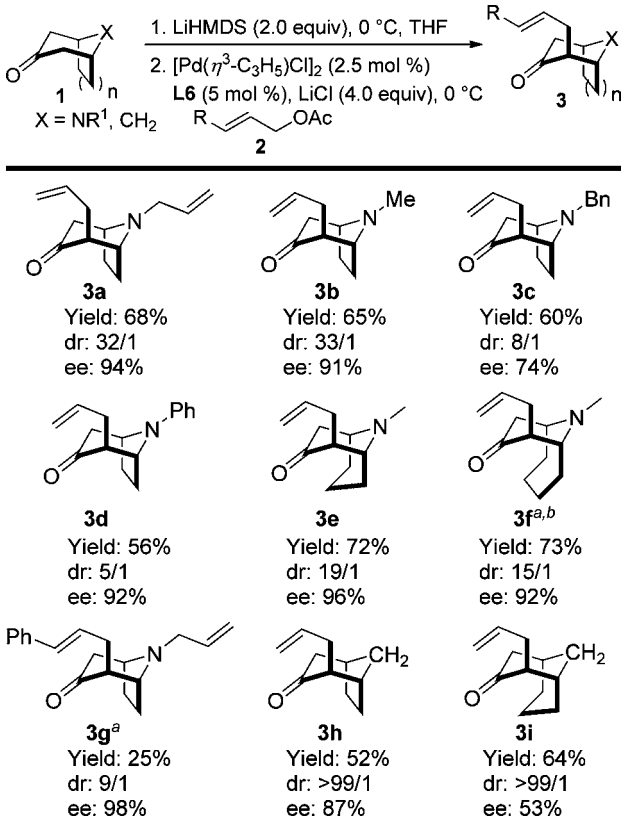


Figure 2. Substrate scope for desymmetrization of bicyclo-[3.*n*.1]-3-one by Pd-catalyzed AAA reaction. Molar ratio of [Pd(η^3-C$_3$H$_5$)Cl]$_2$/**L6**/**1**/**2**/LiHMDS/LiCl = 2.5/5/100/150/200/400. Reaction time: 24 h. Isolated yield; ee determined by chiral GC or HPLC. [a] *t*-BuOK used as base. [b] dr of the product **3f** was reduced to 2/1 after purification due to easy epimerization.

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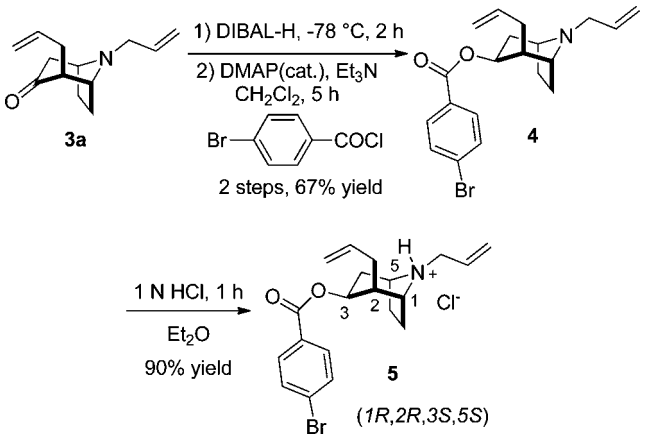
Scheme 1. Conversion of Product **3a** into Compound **5**



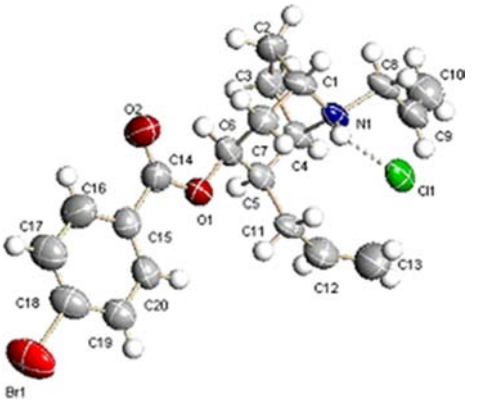


Figure 3. ORTEP drawing of Compound **5**.

excellent ee, and good yield. Unfortunately, the dr was reduced to 2:1 during purification by column chromatgraphy on silica gel due to the easy epimerization of the product **3f**. Cinnamyl acetate was subjected to the reaction with 8-allyl-nortropan-3-one (**1a**) in the presence of *t*-BuOK. The allylation product **3g** was obtained with 9:1 dr and 98% ee; however, the yield was only 25%. The low yield is attributable to a low conversion. Other types of bicyclic ketones were also examined. It is interesting to note that the reaction led to excellent diastereomeric and enantiomeric ratios when bicyclo[3.2.1]octan-3-one was used (**3h**). However, lower enantioselectivity was observed from the reaction with bicyclo[3.3.1]nonane-3-one as the substrate (**3i**). A 1,3-disubstituted allylic acetate, (*E*)-1,3-diphenylallyl acetate, was reacted with 8-benzyl-8-azabicyclo-[3.2.1]octan-3-one (**1c**) under optimized reaction conditions. However, no allylic alkylation occurred and compound **1c** was recovered in 91% yield.

Allylated product **3a** was converted to ester **4** by DIBAL-H reduction and esterfication. The reaction of **4** with hydrogen chloride provided **5** (Scheme 1). Its X-ray diffraction analysis showed the absolute configuration of product **5** to be (1*R*,2*R*,3*S*,5*S*) (Figure 3). Accordingly, the allylated product **3a** has the (1*R*,2*R*,5*S*) configuration.

In conclusion, desymmetrization of carbon nucleophiles by palladium-catalyzed asymmetric allylic alkylation has been realized for the first time. The resulting products with three chiral centers were obtained in good yield and with high diastereo- and enantioselectivity. The ferrocene-based SIOCPhox ligand proved to be highly effective. The method provides efficient access to chiral tropane derivatives, which may find application in the enantioselective synthesis of tropane alkaloids. Further investigations into the reaction scope and identifying possible applications of the methodology in organic synthesis are underway.

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Supporting Information Available. Experimental procedure, spectral data of compounds **3**–**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.