JOC*Note*

Catalytic Asymmetric Carbalkoxyallylation of Imines with the Chiral Bis-π-allylpalladium Complex

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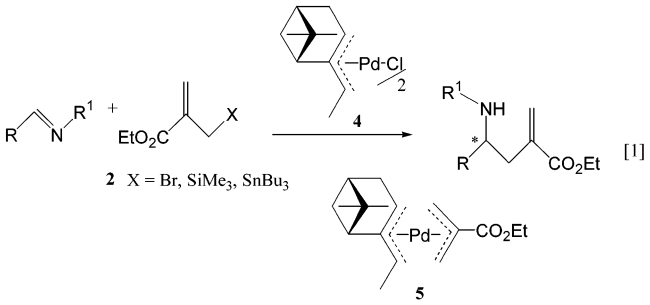
Abstract: Carbethoxyallylstannane was employed along with the bis-π-allylpalladium complex to achieve a useful conversion of prochiral imines to chiral 2-(2-aryl-2-aminoethyl)acrylates which are improtant building blocks for further asymmetric synthesis of a wide range of compounds.

Asymmetric allylation of imines by using catalytic transition metals with chiral ligands is a new frontier of the enantioselective C−C bond formation. Asymmetric allylation of imines or iminium species with unsubstituted allyl donor agents is a widely studied reaction.[1−4] However, little emphasis is given to allylation with the substituted allyl agents especially with methoxy or carbalkoxy groups. Most reports employing the latter reagent result in α-methylene-γ-lactams.[5] However, an acyclic precursor (eg. compound **3**, eq 1) could be of wide interest in the asymmetric synthesis of chiral α-methylene-γ-lactams,[6] substituted pyrrolidines, piperidines,[7] and/or 1,4-heterofunctionalized compounds such as 1,4-amino acids, 1,4-amino alcohols, and 1-amino 3,4-epoxides, which would be difficult to produce by other conventional methods.



[1]

In continuation with our interest in asymmetric allylation of imines using the chiral bis-π-allylpalladium complex[8] we wish to report here the carbalkoxyallylation of imines to chiral 2-(2-aryl-2-aminoethyl)acrylates which are useful precursors for a wide range of functionalized compounds. The allylation with a substituted allyl donor agent of type **2** is based on the formation of the bis-π-allylpalladium complex[9] of type **5** (on reaction of **2** with the catalyst **4,** eq 1). This being nucleophilic would then transfer the carbalkoxyallyl group to the imine giving chiral 2-(2-aryl-2-aminoethyl)acrylates (eq 1).

We wished to study the formation of these 2-(2-aryl-2-aminoethyl)acrylates first in racemic form. Most conventional methods are based on the Barbier-type allylation with Zn, Mg, or In metal.[10] There is one example reported of such allylation on *N*-benzyltrifluoroacetaldimine in DMF solvent with Zn and **2** (X = Br) giving the corresponding carbethoxyhomoallylamine (of type **3**) in 75% yield.[10a] However, such reactions on aryl imines at room temperature or higher temperatures predominantly result in the formation of α-methylene-γ-lactams.[5,10] We carried out similar experiments to prepare the racemates and enantiomerically enriched compounds in the reaction of imine **1c** to give the corresponding carbethoxyhomoallylamine **3c** as shown in Table 1. In the initial experiments, reaction of imine **1c** with **2a** (1.2 equiv) in the presence of Zn (1.2 equiv) activated with catalytic TMS-Cl[10a] in DMF solvent failed to give compound **3c** (Table 1, entry 1). On changing the solvent to THF only 10% of **3c** (entry 2) could be isolated, while the major product

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(4) For allylation of *N*-acylhydrazones see: (a) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (b) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610. (c) Hirabayashi, R.; Ogawa, C.; Sugiura, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 9493. (d) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed*. **2001**, *40*, 4491. (e) Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942. (f) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem*. **1999**, *64*, 8054.

(5) (a) Nyzam, V.; Belaud, C.; Zammattio, F.; Villieras, J. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1835. (b) Dembele, Y. A.; Belaud, C.; Villieras, J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 511. (c) Dembele, Y. A.; Belaud, C.; Hitchcock, P.; Villieras, J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 351.

(6) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villieras, J. *Synlett* **1998**, 275.

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(9) Nakamura, H.; Iwama, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun*. **1995**, 1273.

(10) (a) Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Begue, J.-P. *J. Org. Chem*. **2003**, *68*, 6444. (b) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem*. **1999**, *64*, 3376 and references therein.

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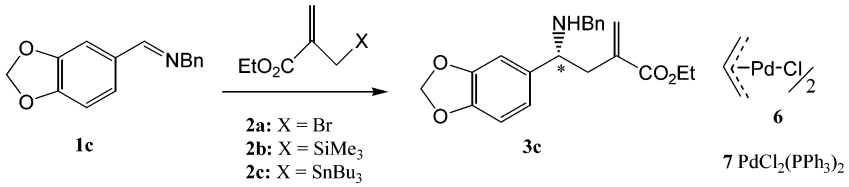
TABLE 1. Optimization of Reaction Conditions for the Following Reaction



entry	allyl agent (equiv)	metal agent[a]	additive (equiv)	solvent	temp (°C)	time (h)	% yield of **3c**	% ee[b]
1	**2a** (1.2)	Zn	TMS−Cl (cat)[c]	DMF	rt	2	messy	
2	**2a** (1.2)	Zn	TMS−Cl (cat.)	THF	rt	2	<10	
3	**2a** (1.2)	Zn	TMS−Cl (cat.)	THF	0	1.5	36	
4	**2b** (1.2)	4	TBAF (0.5)	THF−hexane	0	96	<10	
5	**2c** (1.5)	6		THF	rt	96	messy	
6	**2c** (1.5)	7		THF	rt	144	messy	
7	**2c** (1.5)	4	H_2O (1)	THF	0	192	<10	nd[d]
8	**2c** (1.5)	4	H_2O (1)	THF	5	192	<10	nd
9	**2c** (1)	4	H_2O (1)	THF	*e*	*e*	42	72
10	**2c** (1.5)	4	H_2O (1)	THF	rt	144	32	80
11	**2c** (1.5)	4		THF	rt	168	55	78
12	**2c** (1.5)	4		DMF	rt	168	<15	nd
13	**2c** (1.5)	4	TMS−Cl (cat.)	THF	rt	168	61	80
14	**2c** (1.5)	4	MeOH (1)	THF	rt	144	69	84
15	**2c** (1.5)	4	MeOH (1)	THF	0	168	56	84
16	**2c** (1.5)	4	MeOH (1)	THF	40	24	*f*	

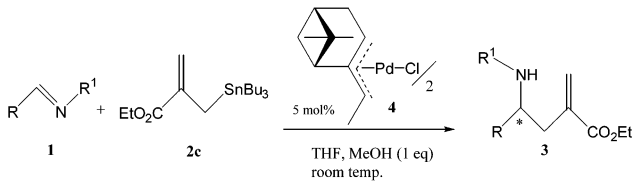
[a] Zn (1.2 equiv.), **4** (5 mol %), **6** (5 mol %), **7** (20 mol %) were used. [b] Ee was determined by HPLC. [c] cat. = catalytic. [d] nd = not determined. [e] Reaction at 0 °C for 96 h followed by room temperature for 96 h. [f] Decomposition of **4** to palladium black.

was the corresponding α-methylene-γ-lactam (45%). In an experiment with the temperature controlled at 0 °C and the time 1.5 h, the product **3c** was isolated in 36% yield besides the usual α-methylene-γ-lactam (24%) being formed (entry 3). Next we tried the silane-based allyl agent **2b** (commercially available) in the presence of fluoride anion[3,8a] (cat. TBAF) and **4** in a mixture of hexane−THF at 0 °C for 96 h. However, the reaction was very sluggish giving only 10% of **3c** (entry 4), while most of the imine was recovered as the corresponding aldehyde after aqueous workup. Reaction of imine **1c** with **2c**[11] (1.5 equiv) in the presence of either **6** or **7** was rather messy with decomposition of the palladium catalyst and failed to give **3c** (entries 5 and 6). Thus, we opted for the reaction conditions as in entry 3 (Table 1), in racemate preparation for chiral HPLC analysis. We then moved to chiral catalysis using catalytic **4**. Reaction of imine **1c** with carbethoxyallylstannane **2c** (1.5 equiv) in the presence of **4** (5 mol %) and water[8b] (1 equiv) as additive in THF solvent at 0 °C for 192 h resulted in only around 10% of **3c** (entry 7). The same conditions were repeated in a reaction at 5 °C for 192 h with no good yield of **3c** (entry 8). The imine **1c** was recovered as aldehyde after aqueous workup. In another experiment similar conditions were repeated at 0 °C for 96 h followed by stirring the reaction mixture at room temperature for a further 96 h. Under these conditions we could isolate 42% of **3c** (entry 9). HPLC analysis indicated 72% ee. Thus, with this success we tried further reactions at room temperature. A room temperature reaction with water as additive met limited success, giving **3c** in 32% yield after a 144-h reaction. The enantiomeric excess increased to 80% (entry 10). A similar reaction without water additive gave an improved yield of **3c** (55%) and 78% ee (entry 11). Changing the solvent to DMF was not effective (entry 12). The imine activation method with TMS-Cl gave **3c** in 61% yield and 80% ee (entry 13). However, this was not a cleaner reaction and other byproducts interfered in the isolation of **3c**. Imine **1c** in the presence of MeOH (1 equiv), **4** (5 mol %), and THF solvent at room temperature for 144 h gave a clean reaction yielding **3c** in a good isolated yield of 69% and 84% ee (entry 14). It was our earlier experience that MeOH[8a] is a good protonating solvent in the catalytic cycle giving shorter reaction time and better yields. The similar reaction at 0 °C was rather slow and after 168 h only 56% of **3c** could be isolated with a similar level of enantioselectivity obtained at the room temperature reaction (entry 15). A reaction at 40 °C resulted in substantial decomposition of the catalyst **4** giving palladium black (entry 16) with no product formation. Thus, carbethoxyallylstannane **2c** (1.5 equiv), MeOH (1 equiv), and **4** (5 mol %) in THF at room temperature stand out to be the optimum conditions for allylation reaction (entry 14). The slower reaction is attributed to the decrease in nucleophilicity of the allyl group by the electron-withdrawing carbalkoxy group. Thus, the transfer of this group from the bis-π-allylpalladium complex **5** is rather slow. However, in no cases was the transfer of the bulky pinane group from complex **5** observed. Since the reactions are rather neutral, no lactams or any isomerized compounds were isolated.

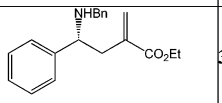
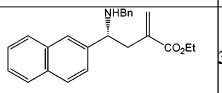
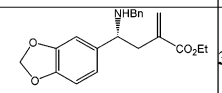
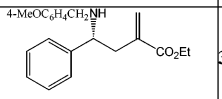
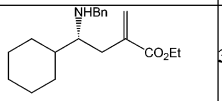
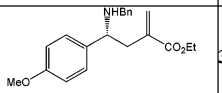
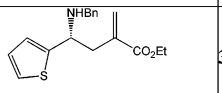
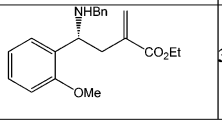
The scope of this allylation protocol with the carbethoxyallylstannane **2c**, chiral π-allylpalladium complex **4,** and MeOH was studied for various imines to furnish the corresponding chiral 2-(2-aryl-2-aminoethyl)acrylates in good yields and enantioselectivities as shown in Table 2. Aryl imines reacted well giving the corresponding carbethoxyhomoallylamines in 63−83% yields and 69−

(11) The carbethoxyallylstannane **2c** was prepared following a literature report, see: Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339.

TABLE 2. Catalytic Asymmetric Carbethoxyallylation of Imines 1 with Stannane 2c, Using Catalyst 4[a]



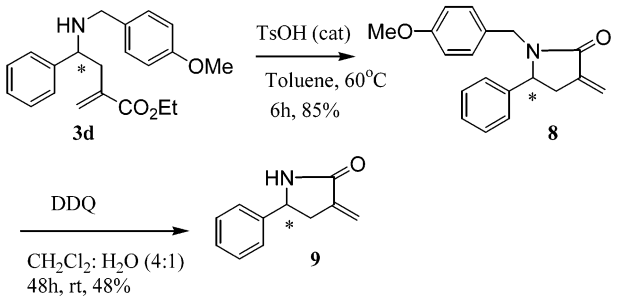
1a R = Ph, R^1 = Bn
1b R = naphthyl, R^1 = Bn
1c R = piperonyl, R^1 = Bn
1d R = Ph, R^1 = -$CH_2C_6H_4OMe$-4
1e R = cyclohexyl, R^1 = Bn
1f R = 4-$MeOC_6H_4$, R^1 = Bn
1g R = thiophenenyl, R^1 = Bn
1h R = 2-$MeOC_6H_4$, R^1 = Bn

entry	imine	time (h)	product[b]		%yield	%ee[c]
1	**1a**	120		**3a**	81	82
2	**1b**	120		**3b**	69	88
3	**1c**	144		**3c**	69	84
4	**1d**	144		**3d**	63	86
5	**1e**	120		**3e**	63	60
6	**1f**	144		**3f**	70	89
7	**1g**	120		**3g**	77	69
8	**1h**	144		**3h**	59	80

[a] All reactions were carried out with carbethoxyallylstannane **2c** (1.5 equiv), **4** (5 mol %), and MeOH (1 equiv) in THF solvent at room temperature for the specified time. [b] Absolute configuration was determined by conversion of compound **3d** into known α-methylene-γ-lactam.[5b] [c] Ee was determined by chiral HPLC.

89% ee values. Aliphatic imine represented by **1e** (Table 2, entry 5) reacted in a good yield of 63% and moderate ee of 60%, which demonstrates that aliphatic imines are poor substrates[8b] in this allylation protocol. The *N*-*o*-methoxybenzylidenebenzylamine **1h** though expected to react faster with the chelating *o*-methoxy group was rather slow in reacting to give **3h** in moderate yield (59%) and 80% ee. Thus, the substituent effect cannot be clearly ascertained.

SCHEME 1. Determination of Absolute Configuration



The reaction is expected to follow a similar mechanistic route as in our earlier allylation using allylstannane[8b] or tetraallylsilane.[8a] The bis-π-allylpalladium complex **5** is formed initially and is a reactive intermediate that is nucleophilic and transfers the carbethoxyallyl group to the imine directed by the chiral pinane skeleton resulting in the observed chiral induction. The electron-withdrawing ester group decreases the nucleophilicity of this allyl transfer resulting in slower reaction. However, in this situation the transfer of the bulky pinane allyl group was not observed, which is a remarkable feature. The reaction is highly efficient in giving the chiral acrylates and no γ-lactams or double bond isomerized compounds were detected, probably due to the neutral conditions involved.

To determine the absolute stereochemistry of this reaction the carbethoxyhomoallylamine **3d** was easily cyclized[6] to the α-methylene-γ-lactam **8** as shown in Scheme 1. The oxidative deprotection[12] of the *p*-methoxybenzyl group gave the lactam **9** having $[\alpha]^{22}_D$ −14.9 (*c* 0.45, $CHCl_3$). This matches with the $[\alpha]^{26}_D$ −17 (*c* 1.35, $CHCl_3$) of (*R*)-**9**.[5b] Thus the products obtained here are expected to have the *R* configuration.

In conclusion we have employed a carbethoxyallylstannane using the bis-π-allylpalladium complex to achieve a useful conversion of prochiral imines to chiral 2-(2-aryl-2-aminoethyl)acrylates. These are important building blocks for further asymmetric synthesis of a wide range of compounds. The Pd-catalyzed asymmetric allylation proceeds under essentially neutral conditions in contrast to the Lewis acid-catalyzed reaction, making it feasible to isolate the desired acrylates and no lactams were formed. Further application of this reaction as well as the products toward asymmetric synthesis of bioactive natural products is in progress.

Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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