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Pd-catalyzed allylic amination in supercritical carbon dioxide: Synthesis of carborane-containing terpenoids

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ABSTRACT

Pd-catalyzed amination of allylic carbonates with *N*-(*ortho*-carboran-3-yl)-*N*-methylamine was carried out in supercritical CO_2. It has been demonstrated that complete conversion of allylic carbonates to the corresponding carborane amines with excellent regioselectivity may be achieved in $scCO_2$ (170 atm, 60 °C) using $NaHCO_3$ as the acceptor base. The reaction offers a selective method for the preparation of allylic amines and provides a useful approach to new terpenoids.

1. Introduction

One of the main aims of modern synthetic chemistry is the catalytic formation of C-heteroatom bonds. In this context, palladium-catalyzed asymmetric allylic substitution is a useful and highly versatile procedure [1–3]. To achieve the highest levels of reactivity and selectivity in the catalytic reactions, different reaction parameters must be explored and adjusted. In this optimization process, not only a careful selection of the ligand but also reaction conditions, such as temperature, solvents are always important. One of the promising and environmentally friendly solvents is supercritical carbon dioxide ($scCO_2$), as it is nontoxic, inflammable and relatively cheap [4–6]. To the best of our knowledge, the Pd-catalyzed allylation reaction in $scCO_2$ was not documented except for our recent paper describing alkylation of (*E*)-1,3-diphenylallyl acetate with dimethyl malonate [7]. At the same time, there are some successful examples of Pd-catalyzed cross-coupling in $scCO_2$, but they are limited to Heck, Suzuki, Sonogashira and Stille reactions (representative examples see under Refs. [8–11]).

Terpenoids are a large and diverse class of naturally occurring organic chemicals found in all classes of living organisms [12]. Plant terpenoids are used extensively for their aromatic qualities and play a role in traditional herbal remedies. They are currently under investigation by numerous groups for different therapeutic properties [13]. It is interesting that simple terpenes such as *D*-limonene, farnesol, geraniol have been shown to have chemotherapeutic activities toward human cancers ([13] and references cited therein). Other promising agents for the cancer therapy are carboranes [14–17]. The traditional niche of carboranes as high-boron content molecules for boron neutron capture therapy (BNCT) remains an active area of research. BNCT makes use of the cytotoxic neutron capture reaction $^{10}B(^{1}n, ^{4}He)^{7}Li$, in which an alpha particle and a lithium ion are produced releasing enough energy to kill the tumor cells [16]. Boron is accumulated in cancer cells when suitable boron compounds are administered, and subsequent radiotherapy with slow neutrons results in the $^{10}B(^{1}n, ^{4}He)^{7}Li$ reaction. The limiting factor in the development of these agents is the delivery of a sufficient boron load selectively to the desired site without peripheral toxicity [14]. For this purpose carboranes can be functionalized to enhance boron delivery. For example, carboranes have been incorporated into porphyrins, dendrimers, amino acids, cholesterol and numerous other molecules [17]. Here, we report our results using $scCO_2$ as an environmentally benign solvent for the regioselective Pd-catalyzed allylation of *N*-(*ortho*-carboran-3-yl)-*N*-methylamine.

2. Experimental

2.1. General

1,3-Diaza-2-methoxy-3-phenyl-2-phosphabicyclo[3.3.0]octane (**L_3**), *N*-(*ortho*-carboran-3-yl)-*N*-methylamine and allylic carbonates **1**–**3** were prepared as published [18–21].

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2.2. Pd-catalyzed allylic amination in $scCO_2$

The catalysts were prepared by adding the corresponding monodentate ligand (0.02 mmol) to a solution of $[Pd(allyl)Cl]_2$ (3.6 mg, 0.01 mmol) in CH_2Cl_2 (0.4 mL). The solution was stirred for 5 min before removing the solvent *in vacuo*. The pre-formed catalyst (0.01 mmol), corresponding allylic carbonate (**1**–3, 0.5 mmol), *N*-(*ortho*-carboran-3-yl)-*N*-methylamine (**4**, 0.5 mmol), and, in several cases, $NaHCO_3$ or K_2CO_3 (1 mmol), H_2O (18 mg, 1 mmol) were placed open to air into a 10 ml autoclave. The vessel was pressurized with $scCO_2$ by means of a syringe-press. The mixture was allowed to equilibrate to the reaction temperature (15 min) and stirred for 14–20 h. After stirring, the vessel was cooled to 10 °C and slowly depressurized. The reaction products were dissolved in CH_2Cl_2 (3 mL), the catalyst removed via a short silica gel column. The filtrate was concentrated *in vacuo* and the products were analyzed by ^{1}H NMR. The amines **5**–**7** may be additionally purified by bulb-to-bulb distillation *in vacuo*.

2.2.1. N-Cinnamyl-N-(ortho-carboran-3-yl)methylamine (**5**)

White solid, mp 86–88 °C. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.44–7.22 (m, 5H, Ar), 6.50 (d, J = 15.9 Hz, 1H, CH=), 6.19 (dt, 15.8 Hz, 6.0 Hz, 1H, =C<u>H</u>–CH_2), 3.69 (d, J = 6.0 Hz, 2H, CH_2–N), 3.52 (br. s, 2H, 2CHcarb), 2.68 (s, 3H, CH_3), 3.07–1.25 (m, 9H, BHcarb). ^{13}C {H}NMR ($CDCl_3$, 100.6 MHz): δ = 136.61 (s, C Ar), 131.34 (s, CH allyl), 128.48 (s, 2 CH Ar), 127.44 (s, CH allyl), 126.79 (s, CH, Ar), 126.19 (s, 2 CH, Ar), 55.90 (s, 2CHcarb), 55.60 (s, CH_2 allyl), 38.33 (s, CH_3, Me). ^{11}B {H} NMR ($CDCl_3$, 128.38 MHz): δ = −18.54 (s, 1B), −15.46 (s, 4B), −14.13 (s, 1B), −10.38 (s, 1B), −4.82 (s, 2B), 2.56 (s, 1B). Anal. Calc. for $C_{12}H_{23}NB_{10}$: C, 49.80; H, 8.01; N, 4.84. Found: C, 49.71; H, 8.13; N, 4.71.

2.2.2. N-(3-Methylbut-2-enyl)-N-(ortho-carboran-3-yl)methylamine (**6**)

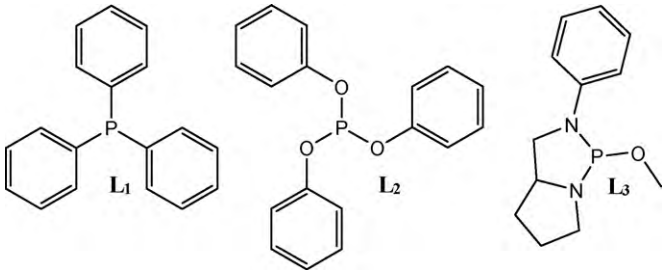
Colorless oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 5.13 (m, 1H, =CH), 3.49 (m, 4H, 2CHcarb and C<u>H</u>$_2$ allyl), 2.58 (s, 3H, CH_3N), 1.72 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.87–1.14 (m, 9H, BH). ^{13}C {H} NMR ($CDCl_3$, 100.6 MHz): δ = 134.65 (s, <u>C</u>=CH), 121.69 (s, C=<u>C</u>H), 55.86 (s, 2CHcarb), 55.88 (s, CH_2), 38.05 (s, CH_3, NMe), 25.72 (s, CH_3, Me), 17.68 (s, CH_3, Me). ^{11}B {H}NMR ($CDCl_3$, 128.38 MHz): δ = −18.75 (s, 1B), −15.58 (s, 4B), −14.20 (s, 1B), −10.49 (s, 1B), −5.02 (s, 2B), 2.73 (s, 1B). Anal. Calc. for $C_8H_{23}NB_{10}$: C, 39.81; H, 9.60; N, 5.80. Found: C, 39.74; H, 9.73; N, 5.69.

2.2.3. (E)-N-(3,7-Dimethylocta-2,6-dienyl)-N-(ortho-carboran-3-yl)methylamine (**7**)

Colorless oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 5.16–5.09 (m, 1H, =CH), 5.09–5.03 (m, 1H, =CH), 3.51 (br. s, 2H, CHcarb), 3.49 (d, J = 6.3 Hz, 2H, CH_2–N), 2.58 (s, 3H, CH_3N), 2.11–2.00 (m, 4H, $(CH_2)_2$), 1.66 (s, CH_3, Me), 1.62 (s, CH_3, Me), 1.59 (s, CH_3, Me). ^{13}C {H}NMR ($CDCl_3$, 100.6 MHz): δ = 137.99 (s, <u>C</u>=CH), 131.51 (s, <u>C</u>=CH), 123.80 (s, C=<u>C</u>H), 121.56 (s, C=<u>C</u>H), 55.81 (s, 2CHcarb), 50.78 (s, CH_2N), 39.49 (s, CH_2), 38.02 (s, CH_3, NMe), 26.19 (s, CH_2), 25.56 (s, CH_3, Me), 17.55 (s, CH_3, Me), 15.93 (s, CH_3, Me). MHz): δ = −18.75 (s, 1B), −15.58 (s, 4B), −14.20 (s, 1B), −10.49 (s, 1B), −5.02 (s, 2B), 2.73 (s, 1B). ^{11}B {H}NMR ($CDCl_3$, 128.38 MHz): δ = −18.62 (s, 1B), −15.49 (s, 4B), −14.19 (s, 1B), −10.47 (s, 1B), −5.04 (s, 2B), 2.66 (s, 1B). Anal. Calc. for $C_{13}H_{31}NB_{10}$: C, 50.45; H, 10.10; N, 4.53. Found: C, 50.58; H, 9.95; N, 4.61.

3. Results and discussion

The use of phosphorus ligands in catalytic allylic substitution reactions has been reported with a Pd-complex precursor, which generally leads to the formation of linear products with excellent-to-high regioselectivity in organic solvents [22–26]. Accordingly, our initial studies have focused on the amination of (*E*)-cinnamyl ethyl carbonate **1** with *N*-(*ortho*-carboran-3-yl)-*N*-methylamine **4** (Scheme 1) in THF using PPh_3 (**L$_1$**, Scheme 1) as the ligand and $[Pd(allyl)Cl]_2$ as the Pd precursor. Unfortunately, in this case no conversion was observed in 20 h (Table 1, entry 1). To evaluate the effect of temperature with the aim of increasing conversion, temperature was raised from 25 to 60 °C. In this case, only trace amounts of the product were observed (Table 1, entry 2). It should be noted, that 3-*ortho*-carborane unit is not only a bulky group but also strong electron-withdrawing substituent [27] that can significantly reduce nucleophilicity of the amine **4**. Next, we turned our attention to the use of $scCO_2$ as the reaction medium. Using the same catalytic system, $[Pd(allyl)Cl]_2/2PPh_3$, in $scCO_2$ (170 atm, 60 °C) gave the product **5** with moderate conversion (Table 1, entry 3). Changing the CO_2 pressure to the upper (240 atm) or lower (120 atm) values did not show any improvement (Table 1, entries 4 and 5). We have then studied amination of **1** in the presence of $NaHCO_3$ as the acceptor base. In this case, a significant increase in the reaction rate was observed (Table 1, entry 6). It should be noted, that similar observations were reported by Buono and co-workers in the Pd-catalyzed amination of a bicyclic allylic diacetate with *N*-methylaniline in the presence of NEt_3 as the base in THF [28]. We also investigated the influence of the nature of the ligands in the amination reaction in $scCO_2$. The prepared palladium catalyst with the more flexible triphenyl phosphite (**L$_2$**, Scheme 1) proves more effective than triphenylphosphine based system (Table 1, entries 6 and 7). Apparently from this, the use of the basic diamidophosphite ligand (**L$_3$**, Scheme 1) showed moderate conversion of **1** (Table 1, entry 8). It should be noted that reaction in all cases occurred with perfect regionselectivity at the less substituted allylic terminus. No other product was obtained. This may be due to high steric bulk of the carborane substituent.



Scheme 1. Phosphorus ligands.

We have also checked the allylic amination of the ethyl prenyl carbonate **2** (Scheme 2). Since triphenyl phosphite as the ligand showed complete conversion of (*E*)-cinnamyl ethyl carbonate **1**,

Table 1
Allylic amination of **1**.

Entry	Ligand	Solvent	T (°C)	P (atm)	Base	t (h)	Conversion of **1** (%)
1	**L$_1$**	THF[a]	25	–	–	20	0
2	**L$_1$**	THF[b]	60	–	–	20	6
3	**L$_1$**	$scCO_2$	60	170	–	14	33[c]
4	**L$_1$**	$scCO_2$	60	240	–	20	27[c]
5	**L$_1$**	$scCO_2$	60	120	–	20	30[c]
6	**L$_1$**	$scCO_2$	60	170	$NaHCO_3$	20	83[c]
7	**L$_2$**	$scCO_2$	60	170	$NaHCO_3$	20	100[c]
8	**L$_3$**	$scCO_2$	60	170	$NaHCO_3$	20	60[c]

[a] 4 ml, 25 °C.
[b] 4 ml, 60 °C.
[c] Only formation of the linear isomer **5** was observed in all cases according to ^{1}H NMR.