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Synthesis of *m*-carboranyl amides via palladium-catalyzed carbonylation

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ABSTRACT

m-Carboranyl amides have been synthesized via the one-pot one-step carbonylation reaction of 1-I-*m*-carborane with primary and secondary amines in the presence of a palladium catalyst and under carbon monoxide atmosphere (Heck reaction). Different catalysts, ligands, bases, and experimental conditions have been evaluated and the results in terms of yield and formation of by-products are discussed.

Dicarba-*closo*-dodecaboranes, generally referred as carboranes, are polyhedral clusters of boron, carbon, and hydrogen atoms with unique physico-chemical properties. Their rich derivative chemistry makes carborane clusters, and particularly dicarba-*closo*-dodecaboranes, suitable building blocks with application for the preparation of macro-molecular and supramolecular entities,[1] nonlinear optics,[2] catalysis,[3] and medicinal chemistry, particularly in the context of BNCT,[4] as hydrophobic pharmacophores of bioactive molecules[5] or as additives in bone cements.[6]

Carboranes exist as *ortho*, *meta*, and *para* isomers (*o*-, *m*-, and *p*-carborane, respectively). Independently of their isomeric form, carboranes can be attached to other molecules either via their carbon or boron atoms. Up to date, functionalization of carboranes at the carbon position has been extensively studied[7] and because of its difficulty, the production of monosubstituted carboranes is especially interesting.[8] One of the commonly used alternatives for the functionalization of carboranes consists in the formation of carboxyl-substituted carboranes via reactions of C-lithio or C-MgBr derivatives with CO_2 followed by acidification.[9] The carboxylic acids can be further converted into the corresponding acid chlorides[10] which in turn can combine with alcohols or amines to form esters[11] or amides,[12] respectively.

Surprisingly, other strategies for the preparation of amides like the Heck carbonylation reaction,[13] which is a powerful method for the synthesis of secondary and tertiary amides by reaction of aryl bromides and vinyl iodides with primary or secondary amines under CO atmosphere in the presence of a palladium complex acting as a catalyst, have not been assayed to date for the preparation of carborane derivatives substituted either at the carbon or boron positions. Such strategy might be anticipated to be suitable for the preparation of carborane derivatives due to the three-dimensional delocalization of skeletal electrons which derive in a three-dimensional aromaticity, as supported by different theoretical investigations.[14]

Recently, we have synthesized and characterized different raclopride (a D_2 receptor antagonist) analogues incorporating *o*- *and m*-carborane in their structures.[5c] Although these carboranyl amides could be successfully synthesized and isolated, the 3 step synthetic strategy (Scheme 1) offered moderate yields while laborious work up was required at each step.

In the current Letter, a method for the palladium catalyzed carbonylation of 1-iodo-1,7-dicarba-*closo*-dodecaborane (**5**) for the one-pot one-step formation of amides is presented for the first time. The reported reaction, employed herein for the preparation of amides, might be used as well for the preparation of other carboxyl-substituted carboranes and could be potentially extended also to the preparation of *o*- and *p*-carboranyl derivatives. Interestingly, the reaction conditions might be also easily translated into the radiochemistry field, where radiosynthetic routes for the preparation of ^{11}C-labeled radiotracers starting from the radioactive precursor [^{11}C]CO have been developed so far.[15] Thus, the biological activity of the resulting radiotracers could be assessed in vivo by using positron emission tomography (PET) a non-invasive, ultra-sensitive molecular imaging technique.

The scheme of the reaction used for the synthesis of carboranyl amides via the Heck carbonylation reaction is shown in Scheme 2. In first instance, we investigated the carbonylation reaction of **5**

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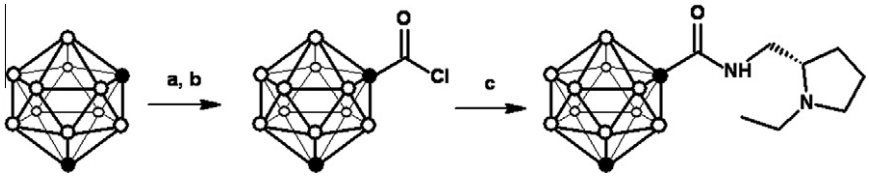
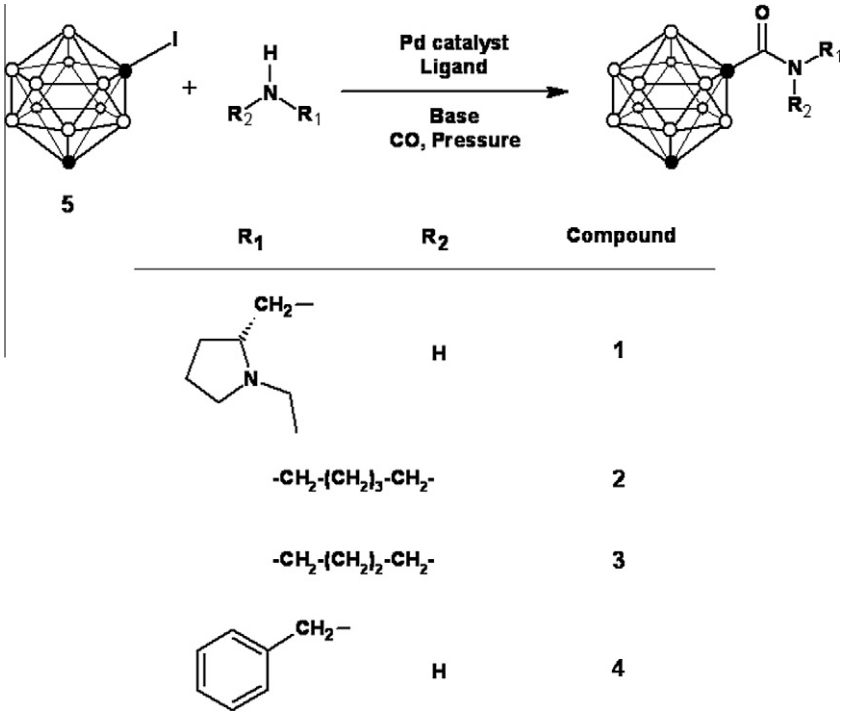


Scheme 1. Synthesis of 1,7-dicarba-*closo*-dodecaboran-1-yl-*N*-{[(2*S*)-1-ethylpyrrolidin-2-yl]methyl}amide (**1**). Reagents and conditions: (a) *n*-BuLi, ether, CO_2, then H_2O; (b) PCl_5, distillation; (c) (*S*)-(−)-2-aminomethyl-1-ethylpyrrolidine.



Scheme 2. Aminocarbonylation reaction of 1-iodo-1,7-dicarba-*closo*-dodecaborane with primary and secondary amines to yield the corresponding amides.

(synthesized following a previously reported method[16] with minor modifications, see Supplementary data for details) with [(2*R*)-1-ethyl-2-pyrrolidinyl]methanamine to yield **1**. In order to assess the effects of the catalyst, the ligand, and the base in the carbonylation reaction, a set of runs was carried out using different catalysts ($Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$), ligands (BINAP, DPPE, DPPF, TPP, Xantphos, and 2,2′-bipyridine) and bases (K_2CO_3, triethylamine, K^{t}OBu, and K_3PO_4) in a carbon monoxide atmosphere at 2 bar.[17]

First screening experiments were performed to choose the most appropriate catalyst. BINAP, a bidentate ligand with a bite angle of 90–91°, was used as a ligand and K_3PO_4 was used as a base. The formation of **1** could not be detected after 2 h of reaction when $Pd_2(dba)_3$, $Pd(OAc)_2$, and $PdCl_2$ were used. Interestingly, formation of the desired product could be observed when $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were used, with chemical conversions of 10.5% and 15.3%, respectively (Table 1, entries 1 and 2). Thus, all subsequent reactions were performed with $Pd(PPh_3)_4$. To assess the effect of the base, different experiments were performed using $Pd(PPh_3)_4$/BINAP as catalyst/ligand. The addition of K_2CO_3 and triethylamine led to moderately lower chemical conversions when compared to K_3PO_4 (Table 1, entries 3 and 4), while the use of K^{t}OBu decreased the reaction rate with respect to K_3PO_4 by a factor of ~30 (entry 5).

To assess the effect of the ligand, the reaction was repeated using DPPF, DPPE, Xantphos, and bipyridine. All combinations led to lower conversion values than those obtained with BINAP (Table 1, entries 2 and 6–9).

The effect of the catalyst and ligand concentrations was also investigated by using $Pd(PPh_3)_4$/BINAP at different molar ratios with respect to compound **5**. As can be seen in Table 1 (entries 2, 10 and 11) higher amounts of catalyst and ligand offered significantly lower chemical conversion values.

The substitution of the iodine atom by bromine in the starting *m*-carborane (**6**) in Table 1 did not lead to improved results (0.7% conversion after 2 h reaction, entry 12) while no desired compound could be detected when 1-trifluoromethanesulfonyl-1,7-dicarba-*closo*-dodecaborane (**7**) in Table 1 was used as the starting material (entry 13).

The kinetic profile of the reaction was monitored by GC–MS under optimized conditions, that is, using $Pd(PPh_3)_4$/BINAP/K_3PO_4. The reaction proceeded fast during the first 2 h (chemical conversions of 8.5% and 15.3% after 1 and 2 h, entries 16 and 2, respectively). However, at longer times the reaction rate significantly decreased until a plateau was reached at conversions ~25% (entries 18 and 19). Significant amounts of *m*-carborane could be detected in the chromatograms of the corresponding reaction crudes, suggesting the de-iodination of **5**. In parallel, increasing amounts of the undesired symmetrical urea were observed while increasing the reaction time. The relative formation rate of the urea with respect to the desired amide decreased when the CO pressure was decreased to 1 bar, and increased when the pressure was increased to 10 bar, although chemical conversion for the amide was lower than the one obtained at P = 2 bar (Table 1, entries 2, 14 and 15).

Table 1
Experimental conditions and reaction extent for the synthesis of *m*-carboranyl secondary and tertiary amides via the Heck carbonylation reaction

Entry[a]	Precursor	Catalyst	Amounts of catalyst[b] (equiv)	Ligand	Amount of ligand[b] (equiv)	Base[c]	Reaction time (h)	CO pressure (bar)	% Reaction[d]
1	5	$Pd(PPh_3)_2Cl_2$	0.02	BINAP	0.04	K_3PO_4	2	2	10.5
2	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	2	2	15.3
3	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_2CO_3	2	2	4.3
4	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	Triethylamine	2	2	5.2
5	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K^tOBu	2	2	0.4
6	5	$Pd(PPh_3)_4$	0.02	DPPF	0.04	K_3PO_4	2	2	1.7
7	5	$Pd(PPh_3)_4$	0.02	DPPE	0.04	K_3PO_4	2	2	3.2
8	5	$Pd(PPh_3)_4$	0.02	Xantphos	0.04	K_3PO_4	2	2	1.5
9	5	$Pd(PPh_3)_4$	0.02	Bipyridine	0.04	K_3PO_4	2	2	2.1
10	5	$Pd(PPh_3)_4$	0.10	BINAP	0.20	K_3PO_4	2	2	7.7
11	5	$Pd(PPh_3)_4$	0.20	BINAP	0.40	K_3PO_4	2	2	1.5
12	6	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	2	2	0.7
13	7	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	2	2	0.0
14	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	2	1	14.4
15	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	2	10	2.1
16	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	1	2	8.5
17	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	4	2	18.1
18	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	16	2	25.3
19	5	$Pd(PPh_3)_4$	0.02	BINAP	0.04	K_3PO_4	24	2	26.7

[a] All reactions were carried out in THF (1 mL) using 25 mg (0.09 mmol) of carborane precursor and 0.15 mmol of amine.
[b] With respect to carborane precursor.
[c] Amount of base: 0.27 mmol.
[d] Chemical conversion as determined by GC–MS.

Optimized experimental conditions (entry 19 in Table 1) were applied to the synthesis of compounds **1**–**4** (Scheme 2). After purification by chromatography (see Supplementary data for details), yields of 21%, 15%, 16%, and 10%, respectively, were obtained. All compounds were characterized by ^1H NMR, $\{^1H–^{11}B\}$ NMR, ^{13}C NMR, ^{11}B NMR, $\{^{11}B–^1H\}$ NMR, $^1H–^{13}C$ HSQC, high resolution mass spectrometry and elemental analysis (see Supplementary data).

In conclusion, we present here an unprecedented strategy for the synthesis of 1-*m*-carboranyl amides via the one-pot one-step reaction of 1-iodo-*m*-carborane with primary or secondary amines under CO atmosphere in the presence of a palladium complex acting as a catalyst. The effects of the catalyst, the ligand, the base, CO pressure, and reaction time have been investigated. Under optimized conditions, slightly lower yields than those previously reported using alternative strategies have been obtained, but both the number of steps and the workup required have been substantially decreased. To the best of our knowledge, the preparation of carboranyl derivatives using the Heck carbonylation reaction has not been reported to date and could be a powerful tool for the synthesis of more complex molecules containing a carborane cage. Moreover, this strategy should be suitable for the preparation of ^{11}C-labeled carboranyl amides using $[^{11}C]CO$ as the labeling agent for further in vivo evaluation using PET. This work will be approached in our lab in the next future.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.019.

References and notes

1. (a) Grimes, R. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1289–1290; (b) Wedge, T. J.; Hawthorne, M. F. *Coord. Chem. Rev.* **2003**, *240*, 111–128; (c) Fox, M. A.; Hughes, A. K. *Coord. Chem. Rev.* **2004**, *248*, 457–476; (d) Andrews, P. C.; Hardie, M. J.; Raston, C. L. *Coord. Chem. Rev.* **1999**, *189*, 169–198; (e) Northrop, B. H.; Yang, H. B.; Stang, P. J. *Chem. Commun.* **2008**, 5896–5908; (f) Puga, A. V.; Teixidor, F.; Sillanpää, R.; Kivekas, R.; Arca, M.; Barberà, G.; Viñas, C. *Chem. -Eur. J.* **2009**, *15*, 9755–9763; (g) Puga, A. V.; Teixidor, F.; Sillanpaää, R.; Kivekäs, R.; Arca, M.; Barberà, G.; Viñas, C. *Chem. -Eur. J.* **2009**, *15*, 9764–9772.
2. (a) Murphy, D. M.; Mingos, D. M. P.; Forward, J. M. *J. Mater. Chem.* **1993**, *3*, 67–76; (b) Murphy, D. M.; Mingos, D. M. P.; Haggitt, J. L.; Powell, H. R.; Westcott, S. A.; Marder, T. B.; Taylor, N. J.; Kanis, V. *J. Mater. Chem.* **1993**, *3*, 139–148; (c) Lamrani, M.; Hamasaki, R.; Mitsuishi, M.; Miyashita, T.; Yamamoto, Y. *Chem. Commun.* **2000**, 1595–1596; (d) Kaszynski, P.; Douglas, A. G. *J. Organomet. Chem.* **1999**, *581*, 28–38; (e) Piecek, W.; Kaufman, J. M.; Kaszynski, P. A. *Liq. Cryst.* **2003**, *30*, 39–48; (f) Kaszynski, P.; Pahomov, S.; Young, V. G. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1061–1083.
3. Hosmane, N. S. In *Boron Science New Technologies and Applications*; CRC Press: New York, 2012; pp 517–577.
4. (a) Hawthorne, M. F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 950–984; (b) Bregadze, V. I.; Sivaev, I. B.; Gabel, D.; Wöhrle, D. *J. Porphyrins Phthalocyanines* **2001**, *5*, 767–781; (c) Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173–230; (d) Barth, R. F.; Coderre, J. A.; Vicente, M. G. H.; Blue, T. E. *Clin. Cancer Res.* **2005**, *11*, 3987–4002; (e) Bregadze, V. I.; Sivaev, I. B. *Eur. J. Inorg. Chem.* **2009**, 1433–1450.
5. (a) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. *J. Med. Chem.* **1999**, *42*, 1501–1504; (b) Ogawa, T.; Ohta, K.; Yoshimi, T.; Yamazaki, H.; Suzuki, T.; Ohta, S.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3943–3946; (c) Vázquez, N.; Gómez-Vallejo, V.; Calvo, J.; Padro, D.; Llop, J. *Tetrahedron Lett.* **2011**, *52*, 615–618.
6. Pepiol, A.; Teixidor, F.; Saralidze, K.; van der Marel, C.; Willems, P.; Voss, L.; Knetsch, M. L. W.; Vinas, C.; Koole, L. H. *Biomaterials* **2011**, *32*, 6389–6398.
7. Bregadze, V. *Chem. Rev.* **1992**, *92*, 209–223.
8. (a) Teixidor, F.; Viñas, C.; Benakki, R.; Kivekäs, R.; Sillanpää, R. *Inorg. Chem.* **1997**, *36*, 1719; (b) Popescu, A.-R.; Musteti, A. D.; Ferrer-Ugalde, A.; Viñas, C.; Núñez, R.; Teixidor, F. *Chem. Eur. J.* **2012**, *18*, 3174–3184.
9. (a) Stanko, V. I.; Klimova, A. I. Zh. *Obshch. Khim.* **1966**, *36*, 165; (b) Stanko, V. I.; Ovsyannikov, N. N.; Klimova, A. I.; Khrapov, V. V.; Shtyrkov, L. G.; Garibov, R. E. Zh. *Obshch. Khim.* **1976**, *46*, 869.
10. (a) Zakharkin, L. I.; Kalinin, V. N.; Zhigareva, G. G. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1970**, 912; (b) Stanko, V. I.; Klimova, A. I.; Brattsev, V. A. Zh. *Obshch. Khim.* **1970**, *40*, 1523.
11. (a) Dikusar, E. A.; Zvereva, T. D.; Kozlov, N. G.; Potkin, V. I.; Yuvchenko, A. P.; Kovganko, N. V. *Russ. J. Gen. Chem.* **2005**, *75*, 575–579; (b) Dikusar, E. A.; Potkin, V. I.; Zvereva, T. D.; Rudakov, D. A.; Yuvchenko, A. P.; Bey, M. P. *Russ. J. Gen. Chem.* **2008**, *78*, 424–428.
12. (a) Reiner, J. R.; Alexander, R. P.; Schroeder, H. A. *Inorg. Chem.* **1966**, *5*, 1460–1462; (b) Zakharkin, L. I.; Ol'shevskaya, V. A.; Boyko, N. B. *Russ. Chem. Bull.* **1996**, *45*, 680–682.
13. Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.
14. (a) Stone, A. J.; Alderton, M. J. *Inorg. Chem.* **1982**, *21*, 2297–2302; (b) Schleyer, P. V. R.; Najafian, K. *Inorg. Chem.* **1998**, *37*, 3454–3470; (c) Gimarc, B. M.; Zhao, M. *Inorg. Chem.* **1996**, *35*, 825–834.
15. Eriksson, J.; van den Hoek, J.; Windhorst, A. D. *J. Labelled Compd. Radiopharm.* **2012**, *55*, 223–228. and references therein.

16. Grafstein, D.; Bobinsky, J.; Dvorak, J.; Smith, H.; Schwartz, N.; Cohen, M. S.; Fein, M. F. *Inorg. Chem.* **1963**, *2*, 1120–1125.
17. Representative experimental procedure: Compound **5** (25 mg, 0.09 mmol) was dissolved in THF (1 mL) and introduced in a glass Tiny-clave (nominal volume: 25 mL). The catalyst, the base, the ligand, and the nucleophile were added, the system was closed, and carbon monoxide was introduced until the appropriate pressure was reached. The reaction mixture was heated under stirring at 85 °C. After 2 h, the reaction was cooled at room temperature, carbon monoxide was flushed, and a sample was analyzed by GC–MS (see Supplementary data for details) to assess the chemical conversion, using reference compound **5** as internal standard.