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Guiding the nitrogen nucleophile to the middle: palladium-catalyzed decarboxylative cyclopropanation of 2-alkylidenetrimethylene carbonates with isocyanates†

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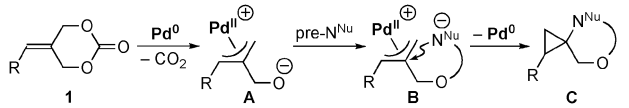
A palladium-catalyzed decarboxylative cyclopropanation of 2-alkylidenetrimethylene carbonates with isocyanates is described to form oxazolidinones of (1-aminocyclopropyl)-methanols with high selectivity. The site of nucleophilic attack is directed by connecting the two reaction components and by employing an electron-deficient triarylphosphine ligand.

Cyclopropanation through a nucleophilic attack at the central carbon of a π-allylpalladium complex was first described by Hegedus and coworkers in 1980 in the context of stoichiometric reactions with ester enolates.[1] Since then, several examples have been reported including catalytic reactions,[2,3] but most of them utilize enolate-based carbon nucleophiles and the selectivity toward cyclopropanation over allylic substitution is not always high enough.[4] In addition, the use of nitrogen-based nucleophiles has been much less explored and is so far limited to the lactam-forming cyclization processes.[5]

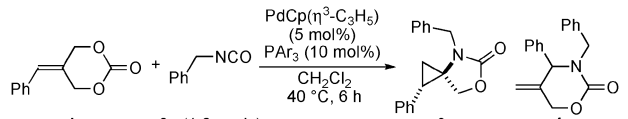
Considering the difficulty of developing a general catalytic method to form cyclopropanes by the attack of nitrogen nucleophiles at the central carbon of π-allylpalladium intermediates while suppressing the well-known allylic amination pathway,[6] here we describe the use of 2-alkylidenetrimethylene carbonates **1**[7] (Scheme 1) toward this goal. This reagent is designed to generate a π-allylpalladium species having an alkoxide tether (**A**) *via* oxidative addition to a palladium(0) catalyst followed by decarboxylation.[7] This then would react with a nitrogen-based pre-nucleophile (pre-N^{Nu}) to form intermediate **B**, thereby guiding the direction of successive nucleophilic attack to the central carbon to form a cyclopropane (**C**) rather than allylic amination products.[8] In this communication, we specifically demonstrate this strategy by employing isocyanates as the pre-nucleophile to form oxazolidinones derived from (1-aminocyclopropyl)methanols with high selectivity. The products obtained here belong to a family of 1-aminocyclopropanecarboxylic acids, which are widely found as structural motifs in various biologically active compounds.[9]



Scheme 1 Schematic representation for the palladium-catalyzed decarboxylative cyclopropanation of 2-alkylidenetrimethylene carbonates **1** with nitrogen-based pre-nucleophiles (pre-N^{Nu}).

In an initial investigation, we prepared 2-benzylidenetrimethylene carbonate (**1a**) as a model reagent in three steps from commercially available 1,3-diacetoxyacetone (eqn (1)). Thus, a Wittig reaction with benzylidene(triphenyl)phosphorane, followed by hydrolysis of the acetates, gave 2-benzylidene-1,3-propanediol in 80% yield over two steps,[10] and treatment of this diol with triphosgene cleanly provided **1a** in 79% yield.[11] Having established a concise synthesis of **1a**, we conducted reactions of **1a** with benzyl isocyanate (**2a**) in the presence of several Pd/2PAr_3 catalysts (5 mol%) in CH_2Cl_2 at 40 °C to realize the strategy outlined above (Scheme 1), and found that the reactivity and selectivity of cyclopropanation *vs.* allylic amination are both highly dependent on the electronic nature of the phosphine ligand (Table 1). Although the use of electron-rich tris(4-methoxyphenyl)phosphine as the ligand gave neither cyclopropanation product **3aa** nor allylic amination product **4aa** (entry 1), both yield and selectivity of **3aa**

Table 1 Palladium-catalyzed decarboxylative cyclopropanation of 2-benzylidenetrimethylene carbonate (**1a**) with benzyl isocyanate (**2a**): effect of phosphine ligand



Entry	Ar	Yield[a] (%)	**3aa**/**4aa**[b]	dr of **3aa**[b]
1	4-$MeOC_6H_4$	0	—	—
2	Ph	27	<1/99	—
3	4-FC_6H_4	41	34/66	>99/1
4	4-$CF_3C_6H_4$	84	92/8	96/4

[a] Combined isolated yield of **3aa** and **4aa**. [b] Determined by ^1H NMR.

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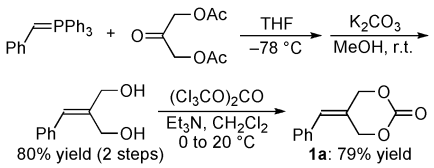
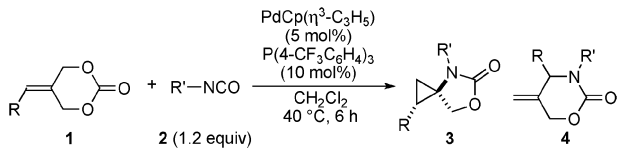
gradually became higher by changing the ligand to more electron-deficient triarylphosphines (entries 2–4), and **3aa** was obtained in high yield with 92% selectivity in the presence of tris(4-trifluoromethylphenyl)phosphine (entry 4). The selective formation of **3aa** with an electron-deficient phosphine ligand is in accordance with our previous observation in the context of lactam-forming reactions using γ-methylidene-δ-valerolactones.[5c]



(1)

Under the conditions using tris(4-trifluoromethylphenyl)-phosphine as the ligand, several 2-arylmethylidenetrimethylene carbonates **1** efficiently undergo decarboxylative cyclopropanation with isocyanate **2a** with high selectivity (**3**/**4** = 88/12 to 98/2, dr = 93/7 to 98/2; Table 2, entries 1–5). The reaction can be easily scaled up to a gram quantity under reduced catalyst loading (2.5 mol%) with a similar efficiency to give **3aa**/**4aa** = 91/9 and dr of **3aa** = 97/3, and the major diastereomer of **3aa** was isolated in 68% yield (eqn (2)). Unsubstituted 2-methylidenetrimethylene carbonate (**1f**) is also applicable to give the cyclopropanation product with perfect selectivity in high yield (entry 6). In addition to these cyclic carbonates, analogous *N*-tosyl carbamate **5** also undergoes the same mode of transformation with isocyanate **2a** to give cyclopropanation product **6**, a spirocyclic imidazolidinone, in 63% yield with no formation of the corresponding allylic amination product (eqn (3)). With regard to the nitrogen substituent of isocyanates, both primary and secondary alkyl groups are tolerated in the reaction with **1a** to give cyclopropanes **3** selectively (**3**/**4** = 84/16 to >99/1, dr = 84/16 to >99/1; entries 7–10). The use of phenyl isocyanate, however, completely reverses the selectivity to give only the allylic amination product (entry 11).[5b,c] The relative configuration of the major diastereomer of **3ca** obtained in entry 3 was established by X-ray crystallographic analysis as shown in Fig. 1.[12]

Table 2 Palladium-catalyzed decarboxylative cyclopropanation of 2-alkylidenetrimethylene carbonates **1** with isocyanates **2**: scope



Entry	**1** (R)	**2** (R′)	Yield[a] (%)	**3**/**4**[b]	dr of **3**[b]
1	**1a** (Ph)	**2a** ($PhCH_2$)	84	92/8	96/4
2	**1b** (4-MeC_6H_4)	**2a**	89	91/9	98/2
3	**1c** (4-ClC_6H_4)	**2a**	91	93/7	98/2
4[c]	**1d** (2-MeC_6H_4)	**2a**	63	98/2	93/7
5	**1e** (2-naphthyl)	**2a**	77	88/12	98/2
6	**1f** (H)	**2a**	93	>99/1	—
7[d]	**1a**	**2b** (4-$MeOC_6H_4CH_2$)	95	93/7	97/3
8	**1a**	**2c** (4-$ClC_6H_4CH_2$)	67	84/16	>99/1
9	**1a**	**2d** (Et)	73	>99/1	88/12
10	**1a**	**2e** (Cy)	70[e]	93/7	84/16
11	**1a**	**2f** (Ph)	82	<1/99	—

[a] Combined isolated yield of **3** and **4** unless otherwise noted. [b] Determined by ^{1}H NMR. [c] 1.5 equiv. of **1d** and 1.0 equiv. of **2a** were used. [d] 1.5 equiv. of **2b** was used. [e] Isolated yield of the major diastereomer of **3**.

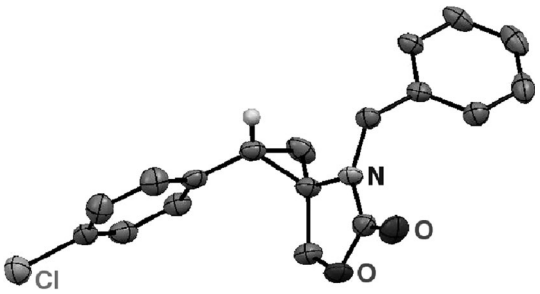
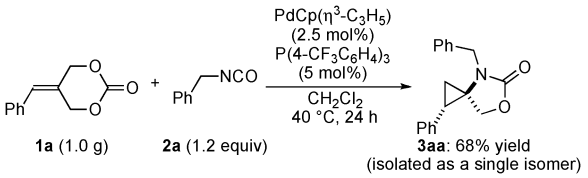
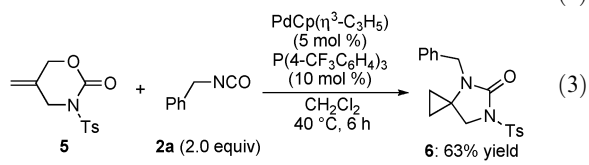


Fig. 1 X-Ray crystal structure of major diastereomer of **3ca** (hydrogen atoms except at the stereocenter are omitted for clarity).

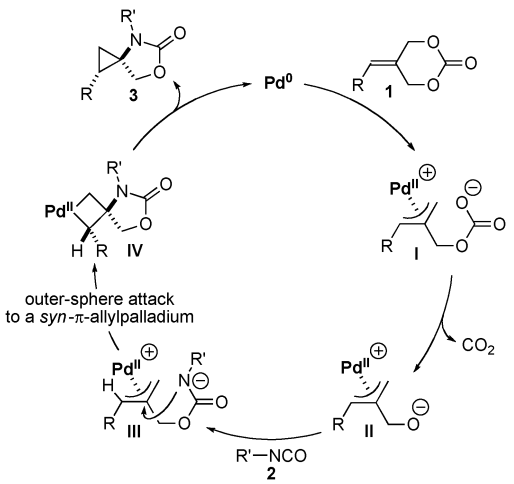


(2)



(3)

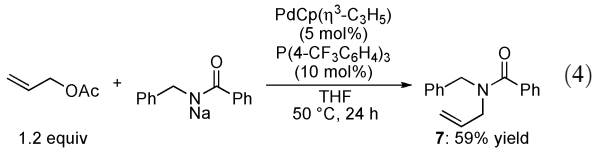
A proposed catalytic cycle of this process is illustrated in Scheme 2. Oxidative addition of the allyl carbonate of **1** to palladium(0) gives π-allylpalladium carbonate **I**. Successive decarboxylation forms π-allylpalladium alkoxide **II**, which then attacks the electrophilic carbon of isocyanate **2** to give intermediate **III**. Ring-closing nucleophilic attack of the nitrogen atom to the central carbon of the π-allylpalladium moiety of **III** leads to palladacyclobutane **IV**.[2d] Reductive elimination releases cyclopropane product **3** along with



Scheme 2 Proposed catalytic cycle for the palladium-catalyzed decarboxylative cyclopropanation of **1** with **2**.

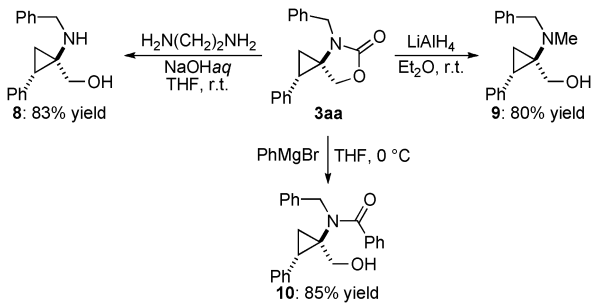
regeneration of a palladium(0) species.[1–3] The step from **III** to **IV** creates two contiguous stereocenters and the observed diastereoselectivity can be explained by an outer-sphere attack of the nitrogen atom to a *syn*-π-allylpalladium species.[13,14]

The guiding effect of the alkoxide tether in the step of nucleophilic attack to the π-allylpalladium in the present catalysis is highlighted in the following intermolecular control experiment. A reaction of allyl acetate with sodium benzoyl-(benzyl)amide under the catalysis of Pd/2P(4-$CF_3C_6H_4$)$_3$ gave exclusively allylation product **7** with no formation of a cyclopropanation product (eqn (4)). This result indicates that connecting two reaction components together in the reaction of **1** and **2** can significantly alter the direction of the nucleophilic attack.



(4)

Cleavage of the tether, namely a ring-opening of the oxazolidinone moiety of **3aa**, can be accomplished in various ways depending on the reaction conditions (eqn (5)). Thus, decarbonylation using ethylenediamine cleanly produces *N*-H aminoalcohol **8** in 83% yield. In contrast, reduction of **3aa** with $LiAlH_4$ gives *N*-methyl aminoalcohol **9** in 80% yield. Furthermore, a nucleophilic ring-opening with phenylmagnesium bromide leads to *N*-benzoyl-protected aminoalcohol **10** in 85% yield.



(5)

In summary, we have described a palladium-catalyzed decarboxylative cyclopropanation of 2-alkylidenetrimethylene carbonates with isocyanates to form oxazolidinones of (1-aminocyclopropyl)methanols with high selectivity. The site of nucleophilic attack has been efficiently directed by connecting the two reaction components and by employing an electron-deficient triarylphosphine ligand. The reaction is also easily scaled up and the products thus obtained can be derivatized to variously substituted (1-aminocyclopropyl)methanols. Future studies will explore further usage of the present strategy including the development of an asymmetric variant of this process.

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Notes and references

1 L. S. Hegedus, W. H. Darlington and C. E. Russell, *J. Org. Chem.*, 1980, **45**, 5193.

2 (*a*) H. M. R. Hoffmann, A. R. Otte and A. Wilde, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 234; (*b*) A. Wilde, A. R. Otte and H. M. R. Hoffmann, *J. Chem. Soc., Chem. Commun.*, 1993, 615; (*c*) A. R. Otte, A. Wilde and H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1280; (*d*) H. M. R. Hoffmann, A. R. Otte, A. Wilde, S. Menzer and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 100.

3 (*a*) M. Formica, A. Musco, R. Pontellini, K. Linn and C. Mealli, *J. Organomet. Chem.*, 1993, **448**, C6; (*b*) A. Satake and T. Nakata, *J. Am. Chem. Soc.*, 1998, **120**, 10391; (*c*) A. Satake, H. Koshino and T. Nakata, *Chem. Lett.*, 1999, 49; (*d*) A. Satake, H. Kadohama, H. Koshino and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 3597; (*e*) R. Shintani, S. Park and T. Hayashi, *J. Am. Chem. Soc.*, 2007, **129**, 14866; (*f*) W. Liu, D. Chen, X.-Z. Zhu, X.-L. Wan and X.-L. Hou, *J. Am. Chem. Soc.*, 2009, **131**, 8734.

4 For examples of obtaining cyclopropanes as a minor product in the palladium-catalyzed allylic alkylation, see: (*a*) C. Carfagna, L. Mariani, A. Musco, G. Sallese and R. Santi, *J. Org. Chem.*, 1991, **56**, 3924; (*b*) C. Carfagna, R. Galarini, A. Musco and R. Santi, *J. Mol. Catal.*, 1992, **72**, 19; (*c*) H. Rudler, P. Harris, A. Parlier, F. Cantagrel, B. Denise, M. Bellassoued and J. Vaissermann, *J. Organomet. Chem.*, 2001, **624**, 186.

5 (*a*) R. Grigg and M. Kordes, *Eur. J. Org. Chem.*, 2001, 707; (*b*) R. Shintani, S. Park, F. Shirozu, M. Murakami and T. Hayashi, *J. Am. Chem. Soc.*, 2008, **130**, 16174; (*c*) R. Shintani, T. Tsuji, S. Park and T. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 7508.

6 For recent reviews, see: (*a*) B. M. Trost and D. R. Fandrick, *Aldrichimica Acta*, 2007, **40**, 59; (*b*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (*c*) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, John Wiley & Sons, Hoboken, NJ, 2002, vol. 2.

7 This type of cyclic carbonate has been employed under palladium catalysis to produce mono-functionalized 2-methylene-1,3-propanediol derivatives: (*a*) I. Shimizu, Y. Ohashi and J. Tsuji, *Tetrahedron Lett.*, 1984, **25**, 5183; See also: (*b*) P. Breuilles and D. Uguen, *Tetrahedron Lett.*, 1987, **28**, 6053; (*c*) S.-K. Kang, D.-C. Park, C.-H. Park and S.-B. Jang, *Synth. Commun.*, 1995, **25**, 1359.

8 For examples of palladium-catalyzed regio-directed allylic substitution reactions, see: (*a*) M. E. Krafft, A. M. Wilson, Z. Fu, M. J. Procter and O. A. Dasse, *J. Org. Chem.*, 1998, **63**, 1748; (*b*) B. M. Trost, R. C. Bunt, R. C. Lemoine and T. L. Calkins, *J. Am. Chem. Soc.*, 2000, **122**, 5968; (*c*) G. R. Cook, H. Yu, S. Sankaranarayanan and P. S. Shanker, *J. Am. Chem. Soc.*, 2003, **125**, 5115 and the references cited therein.

9 For a review, see: F. Brackmann and A. de Meijere, *Chem. Rev.*, 2007, **107**, 4493.

10 This diol can also be obtained in one step from commercially available diethyl benzylidenemalonate by reducing it with (*i*-Bu)$_2$AlH in *ca.* 60% yield.

11 Use of ethyl chloroformate in place of triphosgene gives **1a** in *ca.* 40% yield.

12 CCDC 802126 contains the supplementary crystallographic data for this communication. See also ESI†.

13 The observed stereochemical outcome is consistent with the literature results in the stoichiometric cyclopropanation of *syn*-π-allylpalladium complexes with enolate nucleophiles: ref. 2*c*.

14 For NMR studies of related 1,2-disubstituted π-allylpalladium complexes, see: G. Maglio, A. Musco and R. Palumbo, *Inorg. Chim. Acta*, 1970, **4**, 153.