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Selective Phthalimido-*N*-oxyl (PINO)-Catalyzed C–H Cyanation of Adamantane Derivatives

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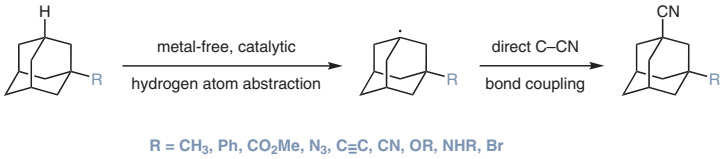

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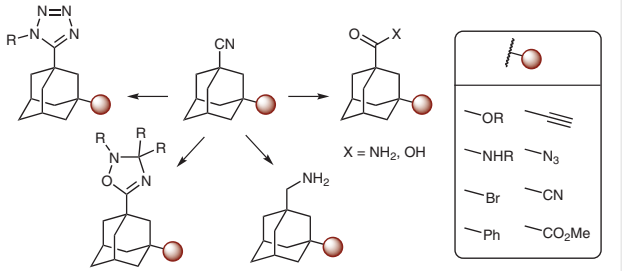
Abstract We present a new method for the selective C(sp^3)–H cyanation of adamantane derivatives with PINO as the hydrogen abstracting reagent. A cyano radical is thereby transferred from *p*-toluenesulfonyl cyanide, allowing the cyanation of adamantane derivatives in up to 71% yield. The protocol presents a novel way to orthogonally functionalized adamantanes that are otherwise difficult to prepare. Mechanistic studies support the hypothesis of a radical pathway.

Key words adamantane, C–H activation, cyanation, *N*-hydroxyphthalimide, NHPI, PINO

Adamantane exhibits fascinating properties, such as rigidity, lipophilicity, steric bulkiness, electron richness, and chemical inertness.[1] By virtue of these desirable features diamondoids, i.e., diamond-like, nanometer-sized aliphatic cage hydrocarbons, for which adamantane is the parent, are used as catalyst backbones,[2] dispersion energy donors,[3] or molecular rectifiers.[4] Adamantane is an attractive moiety in the design of drugs, e.g., memantine and saxagliptin (both belonging to the top 200 drugs by worldwide sales 2016),[5] favorably affecting administration, distribution, metabolism, and excretion (ADME) properties.[6] The selective functionalization of diamondoids is essential for their application, and this presents a formidable challenge in selective sp^3-C–H bond functionalization. Usually hydroxylation, bromination, or amination (*via* Ritter reaction) are used as the first step.[1] The resulting compounds can then readily be functionalized further. However, due to the chemical inertness of unactivated aliphatic C–H-bonds, functionalization requires harsh conditions, making the synthesis of orthogonally disubstituted adamantanes challenging (Scheme 1). A mild direct C(sp^3)–H functionalization of monosubstituted adamantanes would greatly streamline the synthesis of these diamondoids and facilitate their use even more. The incorporation of nitriles is particularly desirable, as they are widely present as key functional groups in a variety of natural products and pharmaceuticals.[7] They can readily be converted into carboxylic acids, esters, amines, or amides. Furthermore, they can be used in [3+2] cycloadditions affording heterocycles such as tetrazoles and oxadiazolines (Scheme 1).[8]

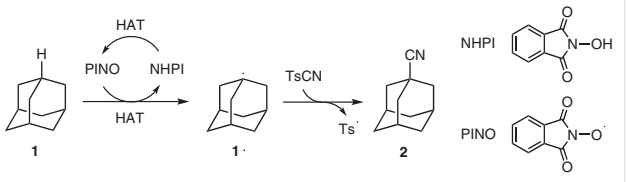


Scheme 1 Orthogonally bifunctionalized adamantane derivatives

Due to the versatility of nitriles, a variety of cyanation methods were developed. While C(sp^2)–H cyanations are well established,[9] C(sp^3)–H cyanations remain challenging. They are often limited to the synthesis of pre-functionalized precursors such as alkyl iodides,[10] allylic compounds,[11] or enolates.[12] Recently, two photocatalytic systems for C(sp^3) cyanation were reported utilizing alkyltrifluoroborates[13] and carboxylates[14] as precursors. Additionally, Sun and coworkers reported an oxidative or free radical C(sp^3)–H cyanation for alkanes, ethers, and tertiary amines.[15] Moreover, cyanations of activated C(sp^3)–H bonds, such as α-heteroatoms[16] and an enantioselective benzylic C–H cyanation[17] have been established. Although some of these methods tolerate a broad range of functional groups, their use is restricted due to elaborate precursor

synthesis. Direct cyanations of unactivated C(sp^3)–H bonds are rare. Only a few direct cyanations exist, including the pioneering studies by Müller and Huber in 1963, who introduced an unselective cyanation with cyanogen chloride[18] and a photoexcited benzophenone mediated C(sp^3)–H cyanation.[19] While the latter approach is applicable to benzylic and aliphatic C–H bonds, the differentiation of these bonds is only modest, due to the use of benzophenone as the hydrogen atom transfer (HAT) reagent. Furthermore, aliphatic substrates often require the use of excess of substrate.

In continuation of our work with phthalimido-*N*-oxyl (PINO),[20] we envisioned a selective C(sp^3)–H cyanation of adamantanes using *N*-hydroxyphthalimide (NHPI).[21] To the best of our knowledge, PINO has never been used in aliphatic C–H bond cyanations.[22] We envisioned a three-step process, consisting of the formation of PINO from its precursor NHPI, followed by HAT from adamantane **1** to PINO, generating an adamantyl radical **1**•, which is trapped by *p*-toluenesulfonyl cyanide (TsCN), thereby affording the desired cyanated product **2** (Scheme 2).

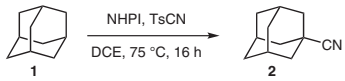


Scheme 2 PINO-catalyzed C(sp^3)–H cyanation concept

We commenced our studies with **1** as a model substrate and *p*-toluenesulfonyl cyanide (TsCN) as the electrophilic cyanide source[23] (Table 1). At first we performed an initial screening to elaborate suitable reaction conditions for the generation of PINO. Systems such as α,α′-azobisisobutyronitrile (AIBN), cobalt (II/III) salts/O_2, and cerium(IV) ammonium sulfate (CAS) afforded only low yields of 1-cyano adamantane **2**[24] and significant amounts of starting material **1** remained. However, cerium(IV) nitrate (CAN)[25] was shown to be superior, resulting in 42% yield of **2**. On the other hand, the use of CAN also led to the formation of significant amounts of 1-nitro adamantane **3**[26] (13%). This side product forms by reduction of Ce(IV) → Ce(III), thus generating HNO_3.[22] HNO_3 itself is capable to generate PINO, thereby releasing $^{\bullet}NO_2$ that recombines with the intermittently formed 1-adamantyl radical.[27] This pathway was confirmed with the use of 1 equiv HNO_3, affording 15% of 1-nitro adamantane **3**.

We envisioned to suppress the formation of **3** by capturing the released HNO_3 (Table 2). Initial screening of bases including MgO, acetates, and carbonates, showed that carbonates performed best. The use of Cs_2CO_3 afforded no product, while Ag_2CO_3, Na_2CO_3, and Li_2CO_3 led to an increase of the yield with up to 77% for Li_2CO_3. In general, the yield increased with decreasing cation radius; 1 equiv Li_2CO_3 worked best. Furthermore, we tested Co(acac)$_3$, a known cocatalyst[28] for PINO, but it was ineffective under the chosen conditions. Importantly, the cyanation selectively proceeds at the tertiary C–H position, thus indicating that PINO performs a chemoselective hydrogen abstraction due to its polarity.[21b]

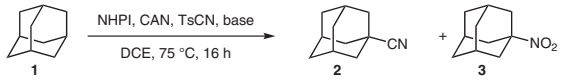
Table 1 Screening of Systems for the PINO-Catalyzed Cyanation[a]



SET reagent	**2** (%)[b]
AIBN[c]	5
Co(acac)$_3$[d]	7
Co(OAc)$_2$[d]	8
CAN[e]	42
CAS[e]	9
HNO_3[e]	47

[a] *Reaction conditions*: 0.5 mmol scale, ratio of **1**/NHPI/TsCN (1:0.1:2), 5 mL 1,2-dichloroethane, 16 h, 75 °C.
[b] Yields determined by GC with hexadecane as internal standard.
[c] 3 mol% AIBN.
[d] 1 mol% of the corresponding metal salt, 1 atm air.
[e] 1 equiv.

Table 2 Influence of Inorganic Bases[a]



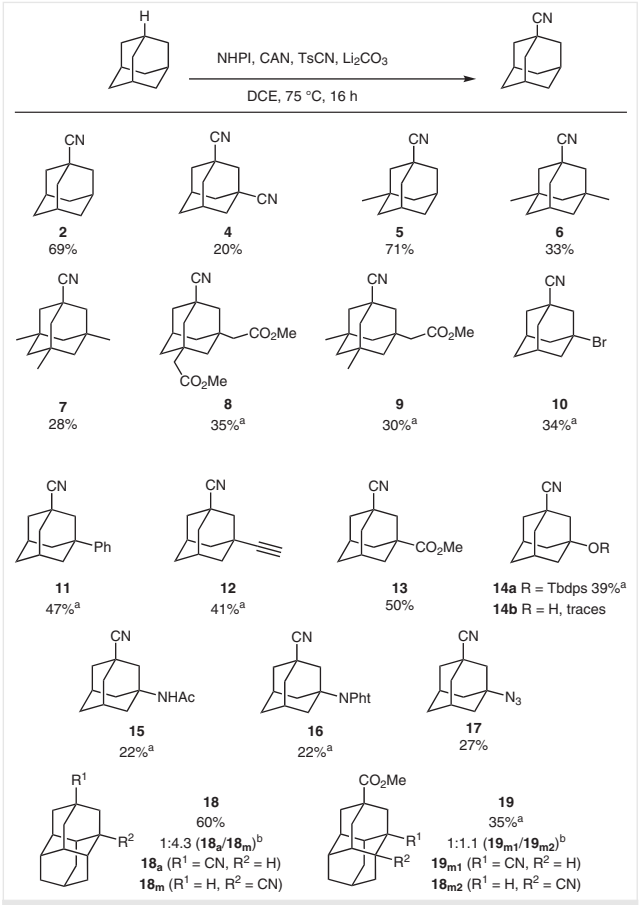
Base (1 equiv)	**2** (%)[b]	**3** (%)[b]
Cs_2CO_3	0	0
Ag_2CO_3	56	<5
Na_2CO_3	73	7
Li_2CO_3	77	5
Li_2CO_3 (1.5 equiv)	47	<5
Li_2CO_3 (0.5 equiv)	51	11
Na_2CO_3[c]	71	8
Na_2CO_3[c,d]	60	14

[a] *Reaction conditions*: 0.5 mmol scale, ratio of **1**/NHPI/CAN/TsCN/base (1:0.2:1:2:1), 5 mL 1,2-dichloroethane, 16 h, 75 °C.
[b] Yields determined by GC with hexadecane as internal standard.
[c] 0.1 equiv NHPI.
[d] 1 mol% Co(acac)$_3$.

With the optimized conditions in hand, we focused on the cyanation of various substrates (Scheme 3). Common C–H activation procedures require excess of the starting material, in order to suppress a second C–H activation of the product. Under our conditions, the cyanation requires only 1 equiv starting material, thereby affording, e.g., 1-cya-

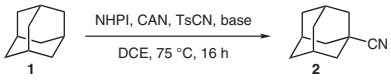
no adamantane **2** in 69% yield without formation of the dicyanated product. The strong electron-withdrawing cyano group deactivates the cage, thus suppressing subsequent cyanation. This was illustrated by utilizing **2**, affording 1,3-dicyano adamantane **4**[29] in only 20% yield. Hence, only 1 equiv substrate is necessary in the cyanation. Methyl adamantane (**5**)[30] was isolated in 71% yield, while dimethyl **6**[31] and trimethyl **7**[32] substituted adamantanes were isolated in 33% and 28% yield, respectively. The same reactivity trend for the corresponding halogenated derivatives was observed by Olah and coworkers in a Lewis acid catalyzed cyanation.[33] The di- and trisubstituted adamantanes were cyanated in comparable yields to the corresponding methyl derivatives, affording cyanated products **8**[34] and **9**.[35] The cyanation of 1-bromo adamantane afforded product **10**[36] in 25% yield, with traces of *N*-tosyloxyphthalimide **S1**,[37] formally a product of the radical recombination of tosylsulfonyl and a PINO radical. Upon addition of 20 mol% NHPI after 6 h the yield of **10** increased to 34%. 1-Cyano-3-phenyl adamantane **11**[38] was obtained in 47% and the alkynyl derivative **12**[39] in 41% yield. Notably, **12** represents an orthogonal building block, containing a triple bond, which is otherwise not easily accessible. Adamantane carboxylic acid methyl ester was cyanated in 50% yield (**13**).[40] Silyl-protected alcohols can be also used under the chosen conditions, affording 39% (**14a**).[41] Use of phthalimides, acetamides, and azides in the cyanation results in the formation of γ-amino acid derivatives **15**–**17**.[42] Note that the use of **17** results in another orthogonally difunctionalized building block readily available for '*click-reactions*'. Furthermore, diamantane can be cyanated in 60% yield, affording **18**[43] in a ratio of 4.3:1 in favor of the medial position. The cyanation of 4-diamantane carboxylic acid methyl ester afforded 35% yield in a ratio of 1:1.1 ($\mathbf{19_{m1}}$:$\mathbf{19_{m2}}$).[44] Particular the syntheses of these cyanated products **19** would require considerably more steps in comparison to established methods.

In order to support our initial mechanistic hypothesis of a radical pathway, several tests were performed (Table 3). In



Scheme 3 Substrate scope of the PINO-catalyzed C(sp^3)–H cyanations. Yields of isolated, pure products are given. *Reaction conditions*: 0.5 mmol starting material, ratio of SM/NHPI/CAN/TsCN/base (1:0.2:1:2:1), 5 mL 1,2-dichloroethane, 16 h, 75 °C. [a] 20 mol% NHPI added after 6 h. [b] Ratio determined by GC-MS.

Table 3 Mechanistic Investigations[a]



Conditions	**2** (%)[b]
NaCN (2 equiv), TBACN (0.15 equiv)	traces (< 1%)
I_2 (1 equiv)	0
0 mol% NHPI	10
dark	40
365 nm	37

[a] *Reaction conditions*: 0.5 mmol scale, ratio of **1**/NHPI/CAN/TsCN/base (1:0.2:1:2:1), 5 mL 1,2-dichloroethane, 16 h, 75 °C.
[b] Yields determined by GC with hexadecane as internal standard.

the presence of a radical scavenger such as I_2, no product formed. The isolation of traces of *N*-tosyloxyphthalimide **S1**, a result of a radical recombination, supports this hypothesis. By performing a control experiment with the optimized conditions (1 equiv TsCN, 1 equiv Li_2CO_3, 0.2 equiv NHPI, 75 °C, 16 h) the formation of **S1** by a nucleophilic substitution could be excluded. In addition, the absence of NHPI afforded only 10% of the cyanated product. This underscores that PINO indeed is the catalytically active species. The exclusion of light decreased the yield to 40% yield. CAN is known to produce nitroxyl radicals upon UV irradiation, while Ce^{IV} is reduced to Ce^{III}.[45] However, irradiation of the reaction mixture at 365 nm afforded only 37% yield of **2**. This result may indicate that low concentrations of nitroxyl radicals facilitate the cyanation, while a higher concentration of $^{\bullet}NO_3$ leads to a higher probability of termination events, consequently lowering the yield. Furthermore, CAN is reduced upon UV irradiation, thus it is not available for the generation of PINO and finally affording a lower yield.

Moreover, the oxidation of the adamantyl radical **1**• to the cation[25,46] could be excluded by the use of a CN^- source (NaCN) in combination with a phase-transfer catalyst (TBACN), affording less than 1% yield.

In summary, we report a novel direct C(sp^3)–H cyanation of adamantane and two diamantane derivatives, utilizing only 1 equiv of substrate.[47] The method allows the efficient synthesis of substituted cyano adamantanes. A variety of these valuable compounds was synthesized for the first time. Mechanistic experiments support a radical mechanism.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610403.

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(30) **1-Cyano-3-methyladamantane (5)**
Yield 0.062 g (0.359 mmol, 71%). R_f = 0.40 (*n*-hexane/EtOAc, 15:1). HRMS (ESI): *m/z* calcd for $C_{12}H_{17}NNa^+$: 198.1253; found: 198.1254 [M + Na^+]$^+$. IR (ATR): 2906, 2850, 2232, 1532, 1456, 1360, 1343, 1162, 1112, 974, 923, 756, 692 cm^{-1}. ^1H NMR (400

MHz, $CDCl_3$): δ = 2.09–2.02 (m, 2 H), 2.00–1.87 (m, 4 H), 1.73 (s, 2 H), 1.64–1.57 (m, 2 H), 1.49–1.41 (m, 4 H), 0.84 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 125.2 (C), 46.4 (C), 42.9 (CH_2), 39.4 (2 CH_2), 35.1 (2 CH_2), 31.0 (CH_2), 30.5 (C), 29.8 (CH_3), 27.9 (2 CH) ppm.

(31) **1-Cyano-3,5-dimethylcyanoadamantane (6)**
Yield 0.031 g (0.164 mmol, 33%). R_f = 0.43 (*n*-hexane/EtOAc, 15:1). HRMS (ESI): *m/z* calcd for $C_{13}H_{19}NNa^+$: 212.1410; found: 212.1412 $[M + Na^+]^+$. IR (ATR): 2902, 2848, 2235, 1455, 1378, 1359, 1342, 1232, 1144, 965, 934, 912, 772, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (hept, *J* = 3.1 Hz, 1 H), 1.86–1.83 (m, 2 H), 1.70–1.59 (m, 4 H), 1.41–1.31 (m, 4 H), 1.17 (s, 2 H), 0.85 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 125.1 (C), 50.1 (CH_2), 45.9 (2 CH_2), 42.2 (2 CH_2), 38.7 (CH_2), 31.8 (C), 30.6 (C), 30.1 (2 CH_3), 28.5 (2 CH) ppm.

(32) **1-Cyano-3,5,7-trimethyladamantane (7)**
Yield 0.028 g (0.138 mmol, 28%). R_f = 0.71 (*n*-hexane/EtOAc, 5:1). HRMS (ESI): *m/z* calcd for $C_{14}H_{21}NNa^+$ *m/z* = 226.1566; found: 226.1563 $[M + Na^+]^+$. IR (ATR): 2948, 2918, 2865, 2843, 2230, 1455, 1377, 1358, 1257, 1233, 912, 788 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.58 (s, 6 H), 1.16–1.02 (m, 6 H), 0.86 (s, 9 H) ppm.^{13}C NMR (101 MHz, $CDCl_3$): δ = 125.0 (C), 49.5 (3 CH_2), 45.3 (3 CH_2), 32.5 (C), 31.5 (3 C), 29.7 (3 CH_3) ppm.

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(34) **1-Cyanoadamantane-3,5-acetic Acid Methyl Ester (8)**
Yield 0.054 g (0.177 mmol, 35%). R_f = 0.23 (*n*-hexane/EtOAc, 3:1). HRMS (ESI): *m/z* calcd for $C_{17}H_{23}NNaO_4^+$: 328.1519; found: 328.1516 $[M + Na^+]^+$. IR (ATR): = 2910, 2857, 2235, 1731, 1438, 1330, 1242, 1162, 1128, 1057, 1022, 851 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 6 H), 2.21–2.17 (m, 1 H), 2.16 (s, 4 H), 1.93–1.87 (m, 4 H), 1.87–1.80 (m, 2 H), 1.62–1.55 (m, 2 H), 1.55–1.46 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2 (2 C), 124.2 (C), 51.5 (2 CH_3), 47.1 (2 CH_2), 45.6 (CH_2), 43.4 (2 CH_2), 39.8 (2 CH_2), 38.5 (CH_2), 33.1 (2 C), 31.6 (C), 28.0 (CH) ppm.

(35) **1-Cyanoadamantane-3-acetic Acid Methyl Ester (9)**
Yield 0.039 g (0.149 mmol, 30%). R_f = 0.08 (*n*-pentane/Et_2O, 10:1). HRMS (ESI): *m/z* calcd for $C_{16}H_{23}NNaO_2^+$: 284.1621; found: 284.1623 $[M + Na^+]^+$. IR (ATR): 2950, 2924, 2900, 2866, 2849, 2232, 1735, 1456, 1356, 1312, 1231, 1192, 1147, 1087, 1012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 2.16 (s, 2 H), 1.76 (s, 2 H), 1.62 (s, 4 H), 1.33–1.20 (m, 4 H), 1.20–1.10 (m, 2 H), 0.88 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (C), 124.5 (C), 51.5 (CH_3), 49.4 (CH_2), 47.2 (2 CH_2), 47.0 (CH_2), 45.2 (2 CH_2), 43.0 (CH_2), 34.06 (C), 32.37 (C), 31.4 (2 C), 29.7 (2 CH_3) ppm.

(36) **1-Cyano-3-bromoadamantane (10)**
Yield 0.040 g (0.167 mmol, 34%). R_f = 0.16 (*n*-pentane/Et_2O, 20:1). HRMS (ESI): *m/z* calcd for $C_{11}H_{14}BrNNa^+$: 262.0202; 262.0204 $[M + Na^+]^+$. IR (ATR): 2948, 2925, 2862, 2228, 1455, 1344, 1330, 1311, 1245, 1121, 1097, 966, 990, 822, 726, 677, 457 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 2 H), 2.35–2.26 (m, 4 H), 2.25–2.17 (m, 2 H), 2.04 (d, *J* = 2.9 Hz, 4 H), 1.75–1.69 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 123.2 (C), 59.6 (C), 50.1 (CH_2), 47.4 (2 CH_2), 38.4 (2 CH_2), 33.9 (CH_2), 33.5 (C), 31.0 (2 CH) ppm.

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(38) **1-Cyano-3-phenyladamantane (11)**
Yield 0.056 g (0.236 mmol, 47%). R_f = 0.23 (*n*-pentane/Et_2O, 20:1). HRMS (ESI): *m/z* calcd for $C_{17}H_{19}NNa^+$: 260.1410; 260.1411 $[M + Na^+]^+$. IR (ATR): = 2926, 2853, 2234, 1599, 1498, 1447, 1343, 1261, 1106, 1080, 1031, 978, 758, 700, 532 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 4 H), 7.25–7.20 (m, 1 H), 2.27–2.23 (m, 2 H), 2.20 (s, 2 H), 2.12–2.04 (m, 4 H), 1.95–1.89 (m, 4 H), 1.80–1.73 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.6 (C), 128.6 (2 CH), 126.5 (CH), 125.0 (CN), 124.7 (2 CH), 45.1 (CH_2), 41.6 (2 CH_2), 39.3 (2 CH_2), 36.0 (C), 35.1 (CH_2), 31.5 (C), 28.1 (2 CH) ppm.

(39) **1-Cyano-3-ethynyladamantane (12)**
Yield 0.038 g (0.204 mmol, 41%). R_f = 0.56 (*n*-hexane/EtOAc, 1:1). HRMS (ESI): *m/z* calcd for $C_{13}H_{15}NNa^+$: 208.1097; 208.1095 $[M + Na^+]^+$. IR (ATR): 3261, 2917, 2857, 2236, 2110, 1726, 1579, 1451, 1345, 1260, 1088, 1014, 869, 795, 688, 50 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 1 H), 2.14 (s, 2 H), 2.13–2.09 (m, 2 H), 1.99 (d, *J* = 3.0 Hz, 4 H), 1.89–1.84 (m, 4 H), 1.70–1.66 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 124.3 (C), 90.2 (C), 68.5 (CH), 44.4 (CH_2), 41.3 (2 CH_2), 39.0 (2 CH_2), 34.6 (CH_2), 30.5 (C), 29.2(C), 27.2 (2 CH).

(40) **3-Cyanoadamantane-1-carboxylic Acid Methyl Ester (13)**
Yield 0.055 g (0.250 mmol, 50%). R_f = 0.47 (*n*-hexane/EtOAc, 3:1). HRMS (ESI): *m/z* calcd for $C_{13}H_{17}NNaO_2^+$: 242.1152; 242.1149 $[M + Na^+]^+$. IR (ATR): 2952, 2915, 2859, 2229, 1720, 1480, 1446, 1346, 1323, 1265, 1240, 1192, 1151, 1125, 1106, 1029, 952, 866, 777, 747, 728, 570, 481, 445 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 2.19–2.13 (m, 4 H), 2.04–1.96 (m, 4 H), 1.93–1.80 (m, 4 H), 1.70 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.2 (C), 124.4 (C), 52.1 (CH_3), 40.7 (CH_2), 40.3 (C), 39.1 (2 CH_2), 37.5 (2 CH_2), 34.8 (CH_2), 30.6 (C), 27.2 (2 CH).

(41) **1-*O*-(*tert*-Butyldiphenylsilyl)-3-cyanoadamantanol (14a)**
Yield 0.080 g (0.193 mmol, 39%). R_f = 0.39 (*n*-hexane/EtOAc, 15:1). HRMS (ESI): *m/z* calcd for $C_{27}H_{33}NNaOSi^+$: 438.2224; found: 438.2226 $[M + Na^+]^+$. IR (ATR): 3071, 2931, 2858, 2235, 1590, 1472, 1455, 1428 1357, 1337, 1316, 1155, 1143, 1110, 1068, 975, 903, 821, 740, 702, 610, 503 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 4 H), 7.45–7.36 (m, 6 H), 2.09 (s, 2 H), 1.99 (s, 2 H), 1.84–1.73 (m, 4 H), 1.70–1.64 (m, 4 H), 1.50–1.37 (m, 2 H), 1.02 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.1 (4 CH), 135.7 (2 C), 129.7 (2 CH), 127.6 (4 CH), 124.2 (C), 71.0 (C), 47.5 (CH_2), 44.3 (2 CH_2), 38.8 (2 CH_2), 34.4 (CH_2), 33.0 (C), 29.9 (3 CH_3), 27.1 (2 CH), 19.3 (C) ppm.

(42) **1-Cyano-3-acetamidoadamantane (15)**
Yield 0.024 g (0.110 mmol, 22%). R_f = 0.46 (CH_2Cl_2/MeOH, 20:1). HRMS (ESI): *m/z* calcd for $C_{13}H_{18}N_2NaO^+$: 241.1311; found: 241.1317 $[M + Na^+]^+$. IR (ATR): 3295, 3078, 2918, 2856, 2232, 1731, 1651, 1548, 1456, 1366, 1307, 1144, 1061, 1007, 702, 602, 541, 452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.32 (s, 1 H), 2.35 (s, 2 H), 2.21 (s, 2 H), 2.11–2.06 (m, 2 H), 2.03–1.93 (m, 4 H), 1.92 (s, 3 H), 1.88–1.80 (m, 2 H), 1.67 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.8 (C), 124.1 (C), 51.0 (C), 42.9(CH_2), 40.3 (2 CH_2), 39.0 (2 CH_2), 34.8 (CH_2), 31.8 (C), 28.5 (2 CH), 24.6 (CH_3) ppm.

1-*N*-Adamantylphthalimide-3-cyano (16)
Yield 0.033 g (0.108 mmol, 22%). R_f = 0.28 (*n*-hexane/EtOAc, 3:1). HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N_2NaO_2^+$: 329.1261; found: 329.1262 $[M + Na^+]^+$. IR (ATR): 2926, 2863, 2226, 1768, 1703, 1611, 1468, 1361, 1341, 1313, 1155, 1111, 1070, 999, 980, 969, 870, 790, 715, 643, 532, 407 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.74 (m, 2 H), 7.72–7.66 (m, 2 H), 2.80 (s, 2 H), 2.58–2.46 (m, 4 H), 2.30 (s, 2 H), 2.14–1.98 (m, 4 H), 1.82–1.66 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.5 (2 C), 134.1 (2 CH), 131.8 (2 C), 124.01 (C), 123.0 (2 CH), 58.6 (C), 41.8 (CH_2), 38.9 (2 CH_2), 38.9 (2 CH_2), 34.6 (CH_2), 32.3 (C), 28.8 (2 CH) ppm.

1-Azido-3-cyano-adamantane (17)
Yield 0.027 g (0.133 mmol, 27%). R_f = 0.13 (*n*-pentane/Et_2O, 20:1). HRMS (ESI): *m/z* calcd for $C_{11}H_{14}N_4Na^+$: 225.1114; found: 225.1111 $[M + Na^+]^+$. IR (ATR): 2919, 2861, 2230, 2087, 1456,

1360, 1339, 1318, 1244, 1130, 1108, 997, 925, 872, 836, 714, 678, 561, 489 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33–2.27 (m, 2 H), 2.04 (s, 2 H), 2.02–1.93 (m, 4 H), 1.84–1.76 (m, 4 H), 1.69–1.63 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 123.6 (C), 57.3 (C), 43.7 (CH_2), 40.1 (2 CH_2), 38.8 (2 CH_2), 34.3 (CH_2), 32.2 (C), 28.9 (2 CH) ppm.

(43) **4-Cyanodiamantane (18a)**

R_f = 0.23 (*n*-pentane/Et_2O, 10:1). HRMS (ESI): *m/z* calcd for $C_{15}H_{19}NNa^+$: 236.1410; found: 236.1411 [M + Na^+]$^+$. IR (ATR): 2908, 2884, 2847, 2228, 1440, 1377, 1358, 1314, 1258, 1126, 1090, 1047, 984, 902, 799, 572, 545, 462 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.03–1.97 (m, 6 H), 1.85 (s, 3 H), 1.83–1.79 (m, 1 H), 1.77–1.74 (m, 3 H), 1.73–1.69 (m, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 125.5 (C), 40.9 (3 CH_2), 37.6 (3 CH_2), 36.4 (3 CH), 36.1 (3 CH), 28.8 (C), 25.4 (CH) ppm.

1-Cyanodiamantane (18m)

R_f = 0.27 (*n*-pentane/Et_2O, 10:1). HRMS (ESI): *m/z* calcd for $C_{15}H_{19}NNa^+$: 236.1410; found: 236.1408 [M + Na^+]$^+$. IR (KBR): 2918, 2889, 2850, 2227, 1636, 1460, 1443, 1340, 1314, 1260, 1057, 1048, 984, 800, 615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23–2.15 (m, 2 H), 2.05–2.00 (m, 2 H), 2.00–1.92 (m, 3 H), 1.87 (s, 3 H), 1.71 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 124.6 (C), 41.4 (CH_2), 39.0 (2 CH), 38.1 (C), 37.7 (CH_2), 37.1 (2 CH_2), 36.6 (2 CH), 36.3 (CH), 35.1 (2 CH_2), 25.6 (CH), 25.0 (CH) ppm.

(44) **1-Cyano-3-diamantane Carboxylic Acid Methyl Ester (19_{m1})**

R_f = 0.13 (*n*-hexane/EtOAc, 10:1). HRMS (ESI): *m/z* calcd for $C_{17}H_{21}NnaO_2^+$: 294.1465; found: 294.1467 [M + Na^+]$^+$. IR (ATR): 2909, 2890, 2858, 2227, 1726, 1463, 1433, 1280, 1254, 1228, 1215, 1133, 1115, 1068, 1033, 985, 889, 846, 790, 767, 739, 709, 632, 507 433, 422 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3 H), 2.22 (s, 1 H), 2.20–2.16 (m, 3 H), 2.01–1.98 (m, 2 H), 1.97–1.94 (m, 2 H), 1.92–1.83 (m, 6 H), 1.77–1.73 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.5 (C), 123.6 (C), 52.1 (CH_3), 42.1 (CH_2), 39.1 (C), 38.8 (2 CH_2), 38.5 (C), 38.2 (2 CH), 37.1 (CH_2), 36.5 (2 CH), 35.3 (CH), 34.3 (2 CH_2), 24.7 (CH) ppm.

1-Cyano-4-diamantane Carboxylic Acid Methyl Ester (19_{m2})

R_f = 0.13 (*n*-hexane/EtOAc, 10:1). HRMS (ESI): *m/z* calcd for $C_{17}H_{21}NnaO_2^+$: 294.1465; found: 294.1462 [M + Na^+]$^+$. IR (ATR): 2906, 2881, 2853, 2224, 1714, 1466, 1444, 1427, 1341, 1321, 1283, 1247, 1221, 1142, 1123, 1091, 1072, 1060, 1045, 1012, 980, 949, 883, 860, 814, 787, 758, 744, 698, 628, 566, 543, 519, 490, 427 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 2.34 (s, 1 H), 2.31 (s, 1 H), 2.10–2.03 (m, 4 H), 1.96 (q, *J* = 3.1 Hz, 1 H), 1.92–1.90 (m, 1 H), 1.89–1.82 (m, 6 H), 1.77–1.72 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.1 (C), 123.9 (C), 52.0 (CH_3), 40.8 (CH_2), 39.4 (CH_2), 38.9 (2 CH), 38.4 (C), 37.3 (C), 36.5 (2 CH_2), 36.5 (2 CH_2), 36.1 (CH), 35.6 (2 CH), 25.3 (CH) ppm.

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(47) **PINO-Catalyzed Cyanations of Adamantane Derivatives – General Procedure**

1 equiv substrate, 2 equiv TsCN, 1 equiv CAN, 1 equiv Li_2CO_3, 0.2 equiv NHPI and 5 mL DCE were stirred for 16 h at 75 °C. The reactions mixture was allowed to cool down to room temperature and filtered over silica gel (50 mL EtOAc, 50 mL MeCN, 50 mL EtOAc).