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Cyanoesterification of 1,2-Dienes: Synthesis and Transformations of Highly Functionalized α-Cyanomethylacrylate Esters

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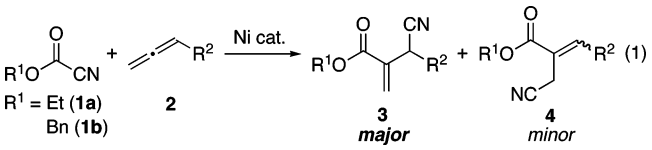
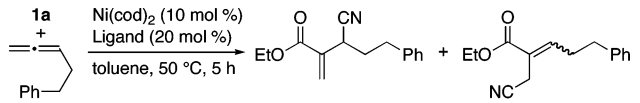
Nitriles are one of the most useful organic compounds, since they are versatile building blocks in organic synthesis and are often seen in many synthetic targets including natural products, pharmaceuticals, and materials.[1] Transition metal-catalyzed cyanofunctionalization reactions of unsaturated compounds have been developed to synthesize variously functionalized nitriles, both cyano and the other functional groups being installed simultaneously in highly stereo- and chemoselective manners.[2,3] Especially the most straightforward and atom economical reaction should be the carbocyanation reaction, which allows direct introduction of organic and cyano groups of nitriles toward unsaturated bonds.[3] We have been interested in the role of nickel catalysts which may activate C−CN bonds[4,5] in an initiation step of the catalytic cycle of the carbocyanation reaction.[3c,d] We report herein nickel-catalyzed cyanoesterification of 1,2-dienes that gives variously functionalized 2-(1-cyanoalk-1-yl)acrylate esters **3** (eq 1).



Initially, we optimized the reaction of 5-phenyl-1,2-pentadiene (**2a**: 1.0 mmol) with ethyl cyanoformate (**1a**: 1.2 mmol) in toluene at 50 °C using $Ni(cod)_2$ and various phosphine ligands (Table 1). Of ligands that we examined, PMe_2Ph was found to be optimal, and ethyl 2-(1-cyano-3-phenylprop-1-yl)acrylate (**3aa**) and (*Z*)-ethyl 2-(cyanomethyl)-5-phenyl-2-pentenoate [(*Z*)-**4aa**] were produced in 77% yield and 10% yield, respectively (entry 1).[6] Although the ratio of **3aa** to **4aa** did not change after prolonged reaction time and/or at higher temperature, the regioselectivity was reversed when the molar ratio of **1a** to **2a** was reversed to 1.0:1.2 (at 50 °C, 3 h; 100 °C, 24 h), giving **4aa** predominantly as a mixture of stereoisomers (entry 2). $PMePh_2$ gave a comparable yield of **3aa** and **4aa** (entry 3), whereas PPh_3 and PMe_3 retarded the reaction (entries 4 and 5). No trace amount of the adduct was obtained with other trialkylphosphines such as PBu_3, PCy_3, and $P(t\text{-}Bu)_3$ as well as $Pd(PPh_3)_4$, a catalyst of choice for the cyanoesterification of norbornene and norbornadiene.[3b]

We propose that **3aa** should be a kinetic product, whereas (*E*)-**4aa** should be a thermodynamic one (entry 1 vs entry 2 of Table 1). The kinetic process may be initiated by oxidative addition of EtOC(O)-CN to Ni(0) (Scheme 1).[4d] The sterically less hindered terminal double bond in **2a** more likely coordinates to the Ni center,[7] and EtOC(O) then migrates to the cumulative carbon of the 1,2-diene to give σ-allylnickel intermediate **7**, which is stabilized by subsequent formation of π-allylnickel complex **8**. Reductive elimination finally should result in formation of **3aa** and regeneration of Ni(0).[8] Formation of regioisomers **4aa** may be understood by coordination of **2a** in an opposite direction followed by similar steps through π-allylnickel **9** or **10**. Under thermodynamic conditions (entry 2 of Table 1), isomerization of **3aa** may take place via a sequence of oxidative addition to Ni(0), isomerization of the resulting π-allylnickel **8** to **9** or **10**, and reductive elimination to give (*E*)- or (*Z*)-**4aa**, which may be in equilibrium with **3aa**. Preferential formation of (*E*)-**4aa** over **3aa** and (*Z*)-**4aa** after longer reaction time at elevated temperature would reflect their thermodynamic stability. In the presence of **1a** in excess (entry 1 of Table 1), the oxidative addition of **3aa** may be slow compared with the favorable oxidative addition of an unreacted **1a**.

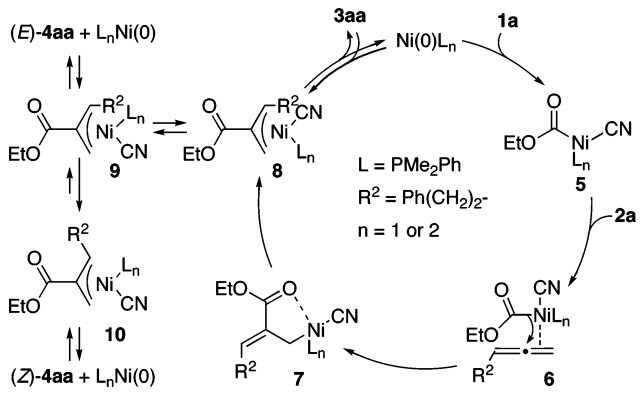
Table 1. Cyanoesterification of 5-Phenyl-1,2-pentadiene (**2a**) Using **1a**[a]



entry	ligand	yield of **3aa** (%)	yield of **4aa** (%) (*Z*:*E*)
1	PMe_2Ph	77[b]	10[b] (>95:5)[c]
2[d]	PMe_2Ph	<5	78[e] (17:83)[c]
3	$PMePh_2$	73[f]	5[f] (>95:5)[g]
4	PPh_3	7[f]	2[f] (50:50)[g]
5	PMe_3	<5[f]	<5[f]

[a] Reactions were carried out using **1a** (1.2 mmol), **2a** (1.0 mmol), $Ni(cod)_2$ (0.10 mmol), and a ligand (0.20 mmol) in toluene (2.0 mL) at 50 °C. [b] Isolated yields based on **2a**. [c] Determined by ^1H NMR. [d] The reaction was carried out using **1a** (1.0 mmol) and **2a** (1.2 mmol) at 50 °C for 3 h and then at 100 °C for 24 h. [e] Isolated yield based on **1a**. [f] Estimated by GC (based on **2a**) using tetradecane as an internal standard. [g] Determined by GC.

Scheme 1. Plausible Catalytic Cycle



We applied the optimized conditions to the cyanoesterification reaction of a diverse range of 1,2-dienes to observe that various allenes having a substituent like a hexyl, cyclohexyl, *tert*-butyl, cyanoalkyl, protected hydroxyalkyl, or *N*-phthalimidoalkyl group underwent the reaction, giving various ethyl 2-(1-cyanoalk-1-yl)-acrylates in good yields (entries 1−7 of Table 2). Benzyl cyanoformate (**1b**) also added across **2a** in an acceptable yield under the identical conditions (entry 8). Disubstiuted allenes such as 3-methyl-1,2-butadiene (**2i**) and 5,6-undecadiene (**2j**) participated in the reaction, albeit in modest yields (entries 9 and 10). We further found

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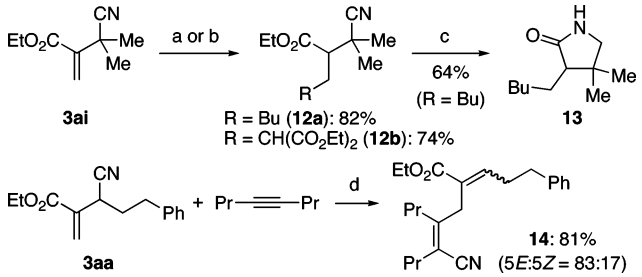
Table 2. Nickel-Catalyzed Cyanoesterification of 1,2-Dienes[a]

entry	1,2-diene (R^2)	time (h)	**3** yield (%)[b]	**4** yield (%)[b]
1	**2b** (*n*-Hex)	5	75 (**3ab**)	9 (**4ab**)[c]
2	**2c** (*c*-Hex)	5	84 (**3ac**)	9 (**4ac**)[c]
3	**2d** (*t*-Bu)	6	70 (**3ad**)	<5 (**4ad**)
4	**2e** [$THPO(CH_2)_2$]	4	62 (**3ae**)	13 (**4ae**)[c]
5	**2f** [*t*-$BuMe_2SiO(CH_2)_2$]	5	64 (**3af**)	14 (**4af**)[c]
6	**2g** [$NC(CH_2)_3$]	5	64 (**3ag**)	15 (**4ag**)[c]
7	**2h** [$PhthN(CH_2)_4$]	4	76 (**3ah**)	15 (**4ah**)[d]
8[e]	**2a**	18	51 (**3ba**)	10 (**4ba**)[f]
9	3-methyl-1,2-butadiene (**2i**)	9	51 (**3ai**)	10 (**4ai**)
10	5,6-undecadiene (**2j**)	24	45 (**3aj**)[c]	—

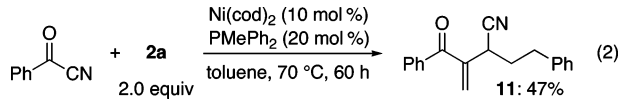
[a] Reactions were carried out using **1a** (1.2 mmol), a 1,2-diene (1.0 mmol), $Ni(cod)_2$ (0.10 mmol), and PMe_2Ph (0.20 mmol) in toluene (2.0 mL) at 50 °C. [b] Isolated yields based on **2**. [c] *Z*:*E* = >95:5 by ^1H NMR analysis. [d] *Z*:*E* = 90:10 by ^1H NMR analysis. [e] Benzyl cyanoformate (**1b**: 1.2 mmol) was used instead of **1a**. [f] *Z*:*E* = 91:9 by ^1H NMR analysis.

Scheme 2. Transformations of the Cyanoesterification Products[a]



[a] Reagents and conditions: (a) BuLi, CuI, $BF_3{\cdot}OEt_2$, Et_2O, −70 °C to rt, 5 h; (b) $NaCH(CO_2Et)_2$, THF, 0 °C to rt, 1 h; (c) $NaBH_4$, $CoCl_2$, EtOH, 0 °C to rt, 9 h; (d) $Ni(cod)_2$ (10 mol %), $P(4\text{-}CF_3{-}C_6H_4)_3$ (20 mol %), CH_3CN, 80 °C, 8 h.

that benzoyl cyanide reacted with **2a** under $Ni/PMePh_2$ catalysis with the same regiochemistry to give benzoylcyanation product **11** in 47% yield (eq 2).[9]



Synthetic versatility of the cyanoesterification products that possess α,β-unsaturated ester and allyl cyanide moieties was examined (Scheme 2). Adduct **3ai** underwent 1,4-addition reactions with butylcopper/$BF_3{\cdot}OEt_2$[10] or sodium malonate to give the corresponding β-cyanoesters **12a** and **12b**, respectively; **12a** further afforded γ-lactam **13** upon treatment with $NaBH_4$ in the presence of $CoCl_2$.[11] Further carbon−carbon bond elongation is possible based on the sequence of carbocyanation reactions. Cyanoesterification product **3aa** successfully added across 4-octyne in the presence of a $Ni(cod)_2/P(4\text{-}CF_3{-}C_6H_4)_3$ catalyst[3d] to regioselectively give trisubstituted acrylonitrile **14** in 81% yield as a mixutre of stereoisomers.

In conclusion, the cyanoesterification reaction of 1,2-dienes is successfully demonstrated using a Ni/PMe_2Ph catalyst. We have achieved regioselective preparation of variously functionalized 2-(1-cyanoalk-1-yl)acrylate esters, which would be potential precursors for γ-aminobutyric acids, β-amino acids, and 1,2-dicarboxylic acids derivatives, and their further transformations including addition reaction across alkynes. Efforts to expand the reaction scope including an enantioselective version as well as synthetic applications are currently in progress in our laboratories.

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Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http:/pubs.acs.org.

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(6) Isomers **3** and **4** obtained in this study are readily separable by a single chromatographic separation on silica gel, demonstrating a practical utility of the present reaction.

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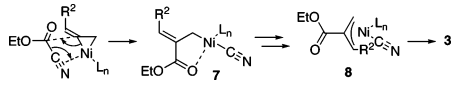
(8) Alternatively, σ-bond methathesis of alkylidene nickelacyclopropane with **1a** to give σ-allylnickel **7** followed by isomerization to π-allylnickel **8** and reductive elimination could also account for the formation of **3**.



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(9) Although the yield was modest, no detectable amount of regioisomers was obtained, and unlike the case of **3aa**, heating the resulting mixture at 100 °C for 24 h after completion of the reaction did not cause the isomerization of **11**.

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