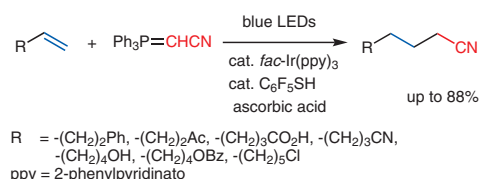


# Photoinduced 1,2-Hydro(cyanomethylation) of Alkenes with a Cyanomethylphosphonium Ylide

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**Abstract** An efficient method has been developed for the 1,2-hydro(cyanomethylation) of alkenes, in which a cyanomethyl radical species is generated from a cyanomethylphosphonium ylide by irradiation with visible light in the presence of an iridium complex, a thiol, and ascorbic acid. The cyanomethyl radical species then adds across the C=C double bond of an alkene to form an elongated alkyl radical species that accepts a hydrogen atom from the thiol to produce an elongated aliphatic nitrile. The ascorbic acid acts as the reductant to complete the catalytic cycle.

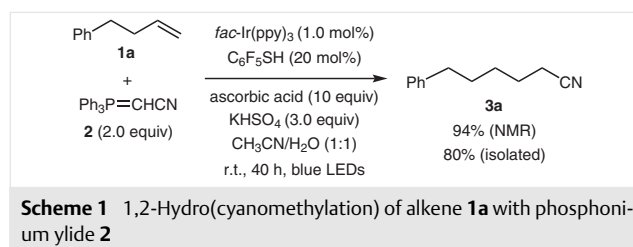
**Key words** alkenes, nitriles, photocatalysis, radicals, phosphonium ylides, hydro(cyanomethylation)

Radical chemistry has undergone a renaissance since the introduction of photoredox catalysis,<sup>1</sup> and a wide variety of reagents are now available as competent precursors to radical species. We recently reported that an ester-stabilized phosphonium ylide<sup>2</sup> can act as a precursor to an (alkoxycarbonyl)methyl radical species<sup>3</sup> when irradiated with visible light in the presence of an iridium catalyst, a thiol, and ascorbic acid.<sup>4</sup> The radical species, substituted by an electron-withdrawing alkoxycarbonyl group, adds across the C=C double bond of an alkene to generate an elongated alkyl radical. Subsequently, the thiol delivers a hydrogen atom to the radical,<sup>5</sup> producing an elongated aliphatic ester.<sup>6</sup>

We also examined the use of a cyanomethylphosphonium ylide instead of an ester-stabilized phosphonium ylide. The former act as the precursor of a cyanomethyl radical species<sup>7–10</sup> that, due to the electron-withdrawing nature of the cyano group, is sufficiently electrophilic to attach to a C=C double bond of an alkene, as in the case of an (alkoxycarbonyl)methyl radical.<sup>3,4,6</sup> The appended alkyl radical

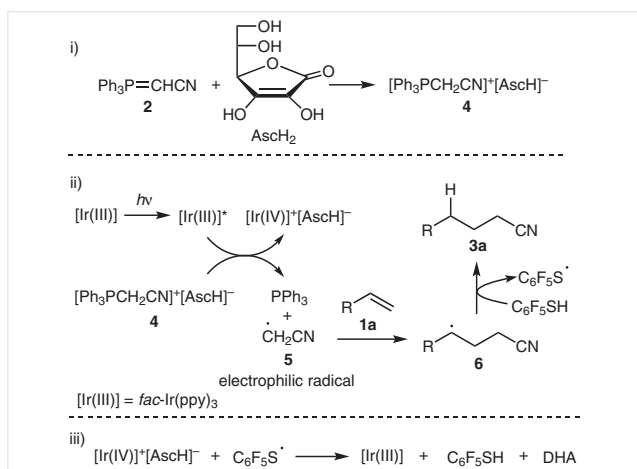
species is not as electrophilic as the original cyanomethyl radical, and can therefore abstract a hydrogen atom from a sulfanyl group<sup>5</sup> to form an elongated aliphatic nitrile.

Initially, we applied the conditions optimized for the reaction of an ester-stabilized phosphonium ylide<sup>4</sup> to the reaction of the cyanomethylphosphonium ylide **2** with 4-phenylbut-1-ene (**1a**), and we obtained 6-phenylhexanenitrile (**3a**) as expected. The yield, however, was moderate (43% by NMR), which led us to adapt the reaction conditions slightly to fit the ylide **2**. The elongated nitrile **3a** was produced in 94% NMR yield and 80% isolated yield when **1a** (0.50 mmol) was treated with **2** (1.0 mmol, 2.0 equiv) in 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O (0.1 M) under irradiation by blue light-emitting diodes (LEDs; 470 nm, 23 W) in the presence of *fac*-Ir(ppy)<sub>3</sub> (1.0 mol%), ascorbic acid (10 equiv), and KHSO<sub>4</sub> (3.0 equiv) at room temperature for 40 hours (Scheme 1). No product resulting from 1,2-addition in the opposite direction was observable within the detection limits of <sup>1</sup>H NMR (400 MHz). A larger-scale experiment using 925 mg (7.0 mmol) of **1a** also gave a comparable yield of **3a** (83% isolated yield), indicating the scalability of the present reaction.



The formation of the product **3a** can be reasonably explained by assuming the radical mechanism depicted in Scheme 2, which is similar to that proposed in the case of ester-stabilized phosphonium ylides.<sup>4</sup> First, an acid/base

reaction of **2** ( $pK_{\text{aH}} = 6.9$ )<sup>11</sup> with ascorbic acid ( $\text{AscH}_2$ ;  $pK_{\text{a}} = 4.0$ )<sup>12</sup> generates the phosphonium ascorbate  $[\text{Ph}_3\text{PCH}_2\text{CN}]^+[\text{AscH}]^-$  (**4**). This has an energetically low-lying  $\sigma^*$  orbital for the C–P linkage. The Ir catalyst  $[\text{fac-Ir}(\text{ppy})_3]$   $[\text{Ir}(\text{III})]$  is photoexcited by visible light to form the excited species  $[\text{Ir}(\text{III})]^*$ . This then transfers a single electron to the  $\sigma^*$  orbital of the phosphonium ascorbate **4**, giving rise to the cyanomethyl radical species **5**, along with  $\text{PPh}_3$  and  $[\text{Ir}(\text{IV})]^+[\text{AscH}]^-$ . Electrophilic addition of **5** to the C=C double bond of alkene **1a** affords the elongated secondary alkyl radical species **6**, which is less electrophilic than **5**. Hydrogen-atom transfer from  $\text{C}_6\text{F}_5\text{SH}$  to **6** produces **3a** and a thiyl radical ( $\text{C}_6\text{F}_5\text{S}^\cdot$ ).<sup>5</sup> The  $[\text{Ir}(\text{IV})]^+$  species and  $\text{C}_6\text{F}_5\text{S}^\cdot$  are reduced back to the  $[\text{Ir}(\text{III})]$  species and  $\text{C}_6\text{F}_5\text{SH}$ , respectively, by the action of the ascorbate anion  $[\text{AscH}]^-$ ,<sup>13,14</sup> which ultimately becomes dehydroascorbic acid (DHA).<sup>15</sup> The additive  $\text{KHSO}_4$  might act by suppressing undesirable formation of a thiolate anion ( $\text{C}_6\text{F}_5\text{S}^-$ ) from  $\text{C}_6\text{F}_5\text{SH}$ .



**Scheme 2** Plausible mechanism for the formation of **3a** from alkene **1a** and phosphonium ylide **2**

Various alkenes **1** were subjected to the 1,2-hydro(cyanomethylation) reaction with **2** (Table 1). A wide range of functional groups were tolerated to afford the corresponding elongated aliphatic nitriles **3b–g** in yields ranging from 74 to 88% (Table 1, entries 1–6). Not only monosubstituted alkenes, but also polysubstituted alkenes, participated in the reaction. Geminally disubstituted alkenes **1h** and **1i** were suitable substrates (entries 7 and 8). Cyclic disubstituted alkenes **1j** and **1k** afforded the corresponding products **3j** and **3k** in yields of 59 and 79%, respectively (entries 9 and 10). The reaction of the acyclic vicinally disubstituted alkenes (*Z*)- and (*E*)-**1l** was sluggish, and the reason for the low yield of product **3l** is unclear (entries 11 and 12). In the case of trisubstituted alkene **1m**, a mixture of diastereomers of **3m** was formed through nonstereoselective transfer of a hydrogen atom to an intermediate tertiary radical

species (entry 13). Even the tetrasubstituted alkene **1n** underwent the reaction (entry 14). The 1,2-adduct **3o** was obtained in 18% NMR yield from styrene (**1o**), and the final reaction mixture contained various products, probably as a result of the high reactivity of the benzylic radical intermediates (entry 15).<sup>16</sup>

**Table 1** 1,2-Hydro(cyanomethylation) of Various Alkenes **1** with Phosphorus Ylide **2**<sup>a</sup>

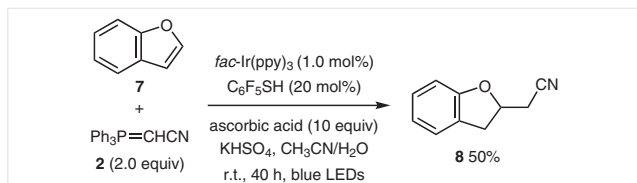
| Entry | Alkene <b>1</b> | Product <b>3</b> | Yield <sup>b</sup> (%) |
|-------|-----------------|------------------|------------------------|
| 1     |                 |                  | 76                     |
| 2     |                 |                  | 82                     |
| 3     |                 |                  | 74                     |
| 4     |                 |                  | 88                     |
| 5     |                 |                  | 77                     |
| 6     |                 |                  | 88                     |
| 7     |                 |                  | 73                     |
| 8     |                 |                  | 77<br>dr = 10:1        |
| 9     |                 |                  | 59                     |
| 10    |                 |                  | 79                     |
| 11    |                 |                  | 28                     |
| 12    |                 |                  | 29 <sup>c</sup>        |
| 13    |                 |                  | 45<br>dr = 7:3         |
| 14    |                 |                  | 56 <sup>c</sup>        |
| 15    |                 |                  | 18 <sup>c</sup>        |

<sup>a</sup> Reaction conditions: **1** (0.50 mmol), **2** (1.0 mmol), *fac*-Ir(*ppy*)<sub>3</sub> (1.0 mol%),  $\text{C}_6\text{F}_5\text{SH}$  (20 mol%), ascorbic acid (5.0 mmol),  $\text{KHSO}_4$  (1.5 mmol), 1:1  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$  (5.0 mL), r.t., 40 h, blue LEDs (470 nm, 23 W).

<sup>b</sup> Isolated yield.

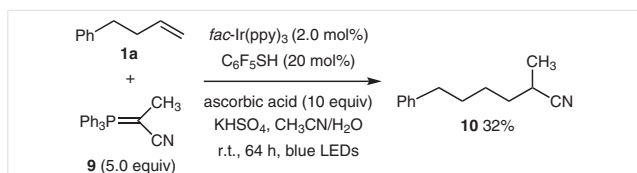
<sup>c</sup> NMR yield with 1,1,2,2-tetrachloroethane as internal standard.

In the case of 1-benzofuran (**7**), the cyanomethyl radical species added regioselectively to form a benzylic radical species, giving the 2-substituted 2,3-dihydro-1-benzofuran **8** (Scheme 3).



**Scheme 3** The addition reaction to 1-benzofuran (**7**)

Notably, even a branched  $\alpha$ -cyanoethyl group was attached to the C=C double bond of **1a** when  $\alpha$ -cyanoethylphosphorus ylide **9** was employed (Scheme 4).



**Scheme 4** The reaction with the  $\alpha$ -cyanoethylphosphonium ylide **9**

A similar reaction to form elongated aliphatic nitriles from alkenes has been reported,<sup>8</sup> in which a cyanomethyl radical species is generated from CH<sub>3</sub>CN by using an excess of dicumyl peroxide at a high temperature; these potentially hazardous conditions significantly limit the synthetic value of the method. The present reaction uses cyanomethylphosphonium ylide, which is stable and easily accessible, as the radical source, thereby providing a convenient method for synthesizing elongated aliphatic nitriles from alkenes.<sup>17</sup>

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1612230>.

## References and Notes

- For reviews, see: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035. (c) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (d) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nat. Rev. Chem.* **2017**, *1*, 0052. (e) Lee, K. N.; Ngai, M.-Y. *Chem. Commun.* **2017**, *53*, 13093. (f) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 10034.
- For photoinduced reactions using phosphonium salts as the radical source, see: (a) Lin, Q.-Y.; Xu, X.-H.; Zhang, K.; Qing, F.-L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1479. (b) Panferova, L. I.; Tsybal, A. V.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2016**, *18*, 996.
- For 1,2-bromo[(ethoxycarbonyl)methylation] of alkenes with BrCH(R)CO<sub>2</sub>Et as the radical source, see: (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (b) Arceo, E.; Montroni, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2014**, *53*, 12064. (c) Cheng, J.; Cheng, Y.; Xie, J.; Zhu, C. *Org. Lett.* **2017**, *19*, 6452. (d) Magagnano, G.; Gualandi, A.; Marchini, M.; Mengozzi, L.; Ceroni, P.; Cozzi, P. G. *Chem. Commun.* **2017**, *53*, 1591. For a recent review, see: (e) Courant, T.; Masson, G. J. *Org. Chem.* **2016**, *81*, 6945.
- Miura, T.; Funakoshi, Y.; Nakahashi, J.; Moriyama, D.; Murakami, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 15455.
- For the use of thiols as sources of electrophilic hydrogen atoms and the subsequent reactions between the resulting thiyl radicals and ascorbate anions, see: Guo, X.; Wenger, O. S. *Angew. Chem. Int. Ed.* **2018**, *57*, 2469.
- For a similar photoinduced elongation of alkenes using BrCH<sub>2</sub>-CO<sub>2</sub>Et as the radical source, see: Sumino, S.; Fusano, A.; Ryu, I. *Org. Lett.* **2013**, *15*, 2826.
- For a review on 1,2-addition reactions with alkanenitriles as radical sources, see: Chu, X.-Q.; Ge, D.; Shen, Z.-L.; Loh, T.-P. *ACS Catal.* **2018**, *8*, 258.
- For 1,2-hydro(cyanomethylation) of alkenes by using CH<sub>3</sub>CN as the radical source, see: (a) Li, Z.; Xiao, Y.; Liu, Z.-Q. *Chem. Commun.* **2015**, *51*, 9969. See also: (b) Bruno, J. W.; Marks, T. J.; Lewis, F. D. *J. Am. Chem. Soc.* **1981**, *103*, 3608. (c) Sonawane, H. R.; Bellur, N. S.; Shah, V. G. *J. Chem. Soc., Chem. Commun.* **1990**, 1603.
- For 1,2-difunctionalization of alkenes by using CH<sub>3</sub>CN as the radical source, see: (a) Bunesco, A.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 3132. (b) Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5443. (c) Lan, X.-W.; Wang, N.-X.; Bai, C.-B.; Lan, C.-L.; Zhang, T.; Chen, S.-L.; Xing, Y. *Org. Lett.* **2016**, *18*, 5986. (d) Wu, X.; Riedel, J.; Dong, V. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11589. (e) Liu, Y.-Y.; Yang, X.-H.; Song, R.-J.; Luo, S.; Li, J.-H. *Nat. Commun.* **2017**, *8*, 14720.
- For 1,2-bromo(cyanomethylation) of alkenes by using BrCH<sub>2</sub>CN as the radical source, see: (a) Voutyritsa, E.; Triandafillidi, I.; Kokotos, C. G. *ChemCatChem* **2018**, *10*, 2466. (b) Voutyritsa, E.; Nikitas, N. F.; Apostolopoulou, M. K.; Gerogiannopoulou, A. D. D.; Kokotos, C. G. *Synthesis* **2018**, *50*, 3395; See also refs. 3 (b) and 3 (d).
- Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968.
- Creutz, C. *Inorg. Chem.* **1981**, *20*, 4449.
- Warren, J. J.; Mayer, J. M. J. *J. Am. Chem. Soc.* **2010**, *132*, 7784.

- (14) For photocatalytic reactions using ascorbic acid as the reductant, see: (a) Maji, T.; Karmakar, A.; Reiser, O. *J. Org. Chem.* **2011**, *76*, 736. (b) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (c) Supranovich, V. I.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2018**, *20*, 840; See also ref. 5.
- (15) Kerber, R. C. *J. Chem. Educ.* **2008**, *85*, 1237.
- (16) The reactions of terminal alkynes such as 4-phenylbut-1-yne gave complex mixtures of products, in which the corresponding 1,2-hydro(cyanomethylation) product (a  $\beta,\gamma$ -unsaturated nitrile) was present in ~10% yield as a 1:1 mixture of *E*- and *Z*-isomers.
- (17) **6-Phenylhexanenitrile (3a); Typical Procedure**  
A vial (2–5 mL; Biotage, Fisher Scientific) equipped with a stirrer bar was charged with the phosphorus ylide **2** (302 mg, 1.00 mmol), *fac*-Ir(ppy)<sub>3</sub> (3.30 mg, 0.005 mmol, 1.0 mol%), ascorbic acid (882 mg, 5.00 mmol), and KHSO<sub>4</sub> (207 mg, 1.52 mmol). The vial was then flushed with argon gas and quickly

capped with a Teflon septum. 4-Phenylbut-1-ene (**1a**, 67.6 mg, 0.51 mmol), C<sub>6</sub>F<sub>5</sub>SH (20.0 mg, 0.100 mmol, 20 mol%), distilled CH<sub>3</sub>CN (2.5 mL), and H<sub>2</sub>O (2.5 mL; degassed with argon gas for 30 min) were added from a syringe, and the mixture was stirred vigorously for 40 h under blue LED lights (470 nm, 23 W) while the vial was cooled with a fan. The mixture was then diluted with brine (25 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to give a residue that was purified by column chromatography [silica gel, hexane/EtOAc (9:1)] to give a colorless oil; yield: 70.7 mg (0.41 mmol, 80%).

IR (ATR): 2936, 2245, 1454 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.45–1.53 (m, 2 H), 1.63–1.73 (m, 4 H), 2.33 (t, *J* = 7.2 Hz, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 7.16–7.21 (m, 3 H), 7.26–7.31 (m, 2 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 17.1, 25.3, 28.3, 30.5, 35.5, 119.7, 125.8, 128.3, 141.9. HRMS (EI<sup>+</sup>): *m/z* [M]<sup>+</sup> calcd for C<sub>12</sub>H<sub>15</sub>N: 173.1204; found: 173.1205.