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COMMUNICATION

# $CO_2$-Enabled Cyanohydrin Synthesis and Facile Iterative Homologation Reactions

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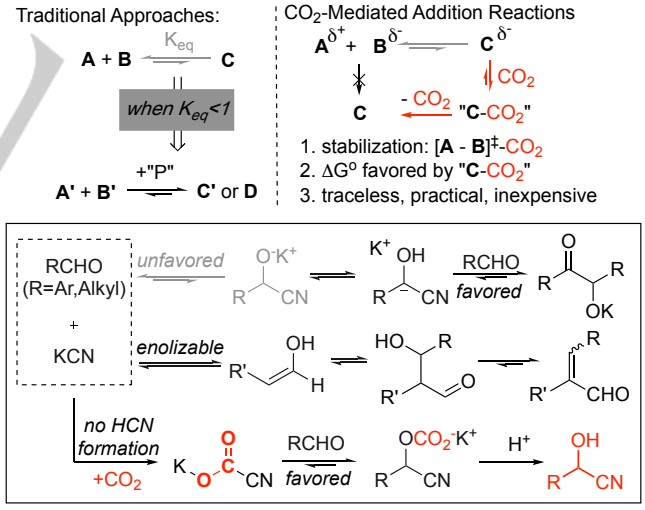
**Abstract:** Thermodynamic and kinetic control of a chemical process is the key to access the desired products and states. Changes are made when a desired product is not accessible; one may manipulate the reaction with additional reagents, catalysts and/or protecting groups. Here we report the use of carbon dioxide to accelerate cyanohydrin synthesis under neutral conditions with an insoluble cyanide source (KCN) without generating toxic HCN. Under inert atmosphere, the reaction is essentially not operative due to the unfavored equilibrium. The utility of $CO_2$-mediated selective cyanohydrin synthesis was further showcased by broadening Kiliani-Fischer synthesis under neutral conditions. This protocol offers an easy access to variety of polyols, cyanohydrins, linear alkylnitriles, by simply starting from alkyl- and arylaldehydes, KCN and an atmospheric pressure of $CO_2$.

A chemical reaction is governed by kinetics and thermodynamics, and a simultaneous control of both parameters is a common practice in designing and optimizing chemical reactions. The manipulation of thermodynamic stability of reactants and products will decide the outcome of a chemical process, while various reaction pathways can lead to undesired products thus reducing overall efficiency of the process.[1] To circumvent unwanted reaction pathways, chemists have developed selective catalysis, protecting groups ("P" in Figure 1), trapping reagents and reactivity-altered reactants (**A'** and **B'**), which in turn can limit the scope and generality of the original reaction. In our ongoing pursuit to implement $CO_2$ in the core of organic synthesis, we sought out ways in which equilibria can be controlled by the use of $CO_2$ – a mild Lewis acid where anionic intermediates can be stabilized.

Carbon dioxide is an intrinsically stable molecule,[2,3] however, it can readily and reversibly react with various nucleophiles.[2,4] Recent applications of carbon dioxide in organic synthesis showed fruitful success particularly in $CO_2$-incorporation,[5] $CO_2$ as a temporal protecting group for C-H activation,[6] $CO_2$ for asymmetric catalysis[7] and oxidation reactions.[8] We recently investigated the role of $CO_2$ in a cyanation reaction,[9] where $CO_2$ can be used in catalytic amounts to facilitate the stereoselective transformation of activated electrophiles via 1,4-conjugate addition reactions. Cyanohydrin synthesis - 1,2-cyanide addition reactions to carbonyls - is one of the oldest C-C bond-forming reactions using HCN as a cyanide source.[10] Despite the high utility of cyanohydrins in organic synthesis[11-14] the use of HCN reduces its application potential due to its volatile nature and health risks. Recent research activities in cyanohydrin synthesis are mainly performed by using TMSCN[15] and cyanoformate[16] as a HCN surrogate.[11,12,17] These reagents suffer from poor atom economy when unprotected cyanohydrins are desired. Furthermore, the cyanation reactions with in-situ generated HCN (from a mixture of TMSCN and an alcohol) are limited by the instability of the cyanide sources thereby limiting the solvent compatibility.[11,18]

Here we demonstrate our strategy in controlling nucleophilic 1,2-addition reactions, namely the cyanohydrin formation reaction, promoted and controlled by $CO_2$. Addition reactions commonly employ nucleophilic reactants which generate anionic intermediates or transition states. The use of electrophilic $CO_2$ can be beneficial when asymmetric binding is realized with $CO_2$; weak interactions with nucleophiles (**B**), and stronger interactions with anionic intermediate, to accelerate the reaction. We confirmed this positive effect of $CO_2$ in practical and scalable cyanohydrin synthesis, which enabled straightforward iterative homologation of an aldehyde with cyanide.




**Scheme 1.** Top; A comparison of traditional reaction optimization and $CO_2$-mediated addition reactions. (**P** = catalysts, protecting groups or trapping reagents); Bottom: cyanohydrin synthesis enabled by $CO_2$/KCN without HCN generation and side reaction pathways.

As summarized in Scheme 1 (bottom), it has been a common knowledge that cyanohydrin formation can not be "catalyzed" due to the high nucleophilicity of cyanides, although the reaction undergoes strong backward reaction ($k_{forward}$ = 1.96 x $10^{-8}$ $sec^{-1}M^{-1}$, $k_{backward}$ = 0.87 x $10^{-10}$ $sec^{-1}$, in RCHO +HCN ↔ RC(OH)CN).[19] Whilst Brønsted acids can generate volatile yet nucleophilic HCN

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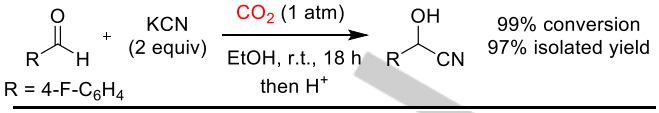
from solid cyanide sources (NaCN or KCN), general and specific acid catalysis can only be operative at exceedingly low concentration of an acid catalyst.[20] This has been manifested in total synthesis, where sophisticated cyanide sources and reagents have been employed. For example, high selectivity towards cyanohydrin formation was mediated by using an activated reagent, i.e. Al-based cyanide sources ($AlEt_2CN$, Nagata's reagent).[21,22] At this juncture, the lack of a general and practical method for cyanohydrin formation reaction under practical and neutral conditions led us to investigate the potential utility of $CO_2$ in cyanohydrin synthesis, which can generate a slightly acidic medium. However, another challenge lays on the side reactions: benzoin- and self-aldol reactions of aldehydes by nucleophilic and basic cyanide (Scheme 1). This is related to the limited scope of Killiani-Fischer synthesis with carbohydrate derivatives. [23] Therefore, we examined the use of $CO_2$ for cyanohydrin formation reactions under practical reaction conditions, to access variety of compounds in a modular fashion.

We have recently shown the applicability cyanohydrins as a nucleophile via an umpolung strategy to access α-keto acids.[24] In the absence of Ti(IV) and DBU, we observed facile formation of cyanohydrin in pseudo first order of the aldehyde with KCN under $CO_2$ atmosphere (1 atm) in ethanol ($k$ = 2.50 x $10^{-3}$). This is approximately $10^5$-folds rate acceleration compared to the reported values without $CO_2$.[19] We verified that the solubility of KCN was increased in the presence of $CO_2$ (Figure S6), owing to the formation of cyanoformate in solution, thus increasing the concentration of available cyanide nucleophiles.[25] To further verify the positive effect of $CO_2$, we performed various control experiments (Table 1). Under $CO_2$ atmosphere (1 atm), full conversion of the starting material (4-fluorobenzaldehyde) was observed to the desired cyanohydrin in quantitative isolated yield (99% conversion, 97% yield). When performing the cyanation under a $N_2$ atmosphere, low conversion to cyanohydrin (7%) was detected within 10 min with no increase in yield of the product after prolonged reaction time (up to 18 h, entry 1, Figure 1 gray circles), indicating the reaction reached fast equilibrium in favor of starting materials with KCN. More importantly, in situ generated HCN gave inferior result, (entry 2, 21% yield), while quantitative yield was obtained with KCN/$CO_2$ combination within 30 minutes (entry 3, 96%, Figure 1 pink circles). A variety of solvents were found to be compatible to induce the desired product under $CO_2$. It is noteworthy here that inferior results were obtained under $N_2$ in all tested solvents compared to under $CO_2$, highlighting the generality of the positive $CO_2$ effect regardless of the choice of solvents (entry 3, i.e. methanol, *n*-heptane, acetonitrile and water, and see Table S1-13 for full optimization). Sodium cyanide is also effective under the standard reaction conditions (entry 5). The solubility of cyanide is important – a soluble cyanide source, ammonium cyanide, showed good conversion to the product with $CO_2$ however, the reaction was not efficient under inert $N_2$ atmosphere (entries 6 and 7). Therefore, the increased solubility of KCN under $CO_2$ is not the sole reason for the observed increase in yield. A common reaction procedure for cyanohydrin synthesis was not comparable in terms of reaction rate: strong acid (e.g. HCl) afforded only low yield of the product because HCN (a "slower" nucleophile) generation is favored (entry 8). The use of acetic acid[26] showed compatible yield (entry 9) confirming that weak acids can indeed promote the reaction without complete protonation of KCN to HCN.

**Table 1.** Optimization of $CO_2$-Mediated Cyanation.[a]




| Entry | Deviation from standard reaction conditions | Yield[b] |
|---|---|---|
| 1 | No $CO_2$ (under $N_2$) | 7% |
| 2 | HCN (2 equiv) instead of KCN | 21% |
| 3 | 30 min of reaction time | 96% |
| 4 | MeOH/water/*n*-heptane/$CH_3CN$/DMF/DMSO instead of EtOH | >85% |
| 5 | NaCN instead of KCN, 30 min | 57% |
| 6 | $NEt_4CN$, 30 min, under $N_2$ | 33% |
| 7 | $NEt_4CN$, 30 min under $CO_2$ | 97% |
| 8 | aq. 5M HCl (4 eq.) instead of $CO_2$ | 24% |
| 9 | AcOH (4 eq.) instead of $CO_2$ | 95% |

[a] 4-fluorobenzaldehyde (1 mmol) and KCN (2 mmol) were mixed in EtOH (2 mL). The reaction mixture was stirred under $CO_2$ (1 atm) for 18 h. [b] Yield was determined by $^{19}F$ nuclear magnetic resonance spectroscopy (NMR) (D1; relaxation time = 2 s) of the crude mixture.

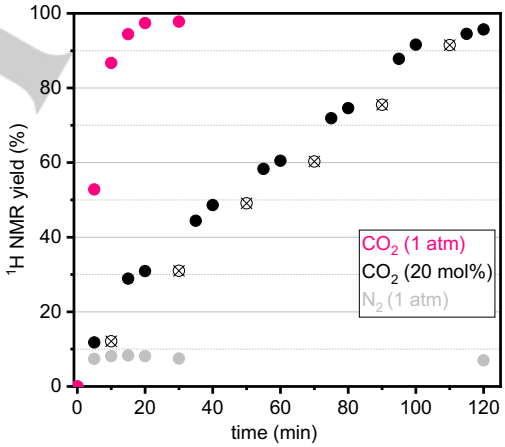



**Figure 1.** Cyanohydrin formation using $CO_2$ (1 atm, pink), sub-stoichiometric amounts of $CO_2$ (6 x 20 mol%, black circles with a cross mark indicate repected injection) and under nitrogen atmosphere (1 atm, gray).

The role of $CO_2$ in the cyanohydrin synthesis was further verified by adding sub-stoichiometric amounts of $CO_2$ (20 mol%) to a reaction mixture repeatedly (Figure 1, black). A sharp increase of product formation was immediately observed followed by the addition of $CO_2$. A near stoichiometric relationship between product formation and the amounts of added $CO_2$ indicates the added $CO_2$ was quantitatively consumed as a stoichiometric reagent.

Having demonstrated the feasibility of the $CO_2$ promoted cyanohydrin formation, we explored the scope of the reaction with respect to both aryl and alkyl aldehydes and ketones (Scheme 2). A variety of aryl aldehydes were tested and provided the corresponding cyanohydrin in excellent yields regardless of their substitution in terms of electron donating and withdrawing

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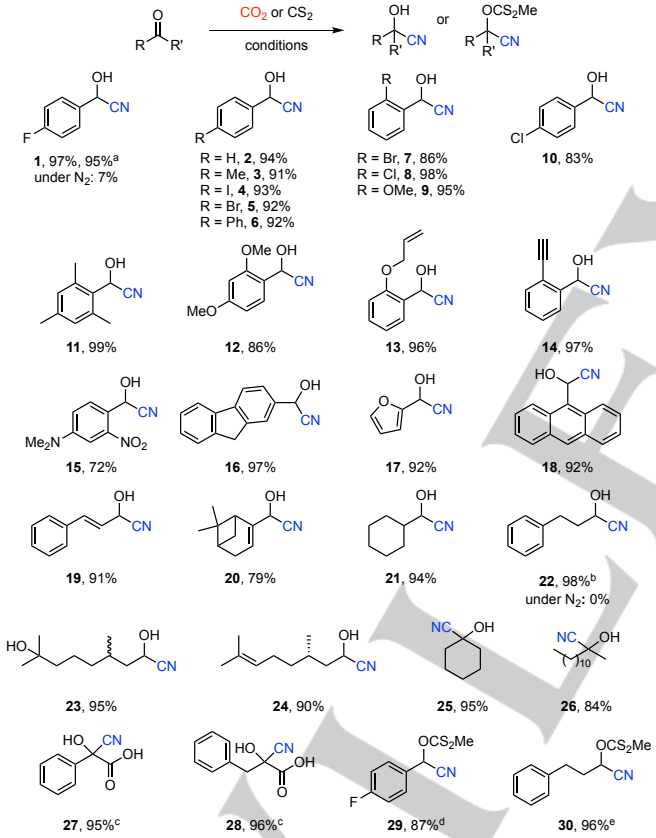
properties. Cyanohydrins of ortho-substituted benzaldehydes showed increased stability,[27] affording high purity products without purification. When subjecting the α,β-unsaturated aldehydes to the reaction conditions the corresponding cyanohydrins (**19** and **20**) was isolated in excellent yields, without the formation of byproduct derived from 1,4-conjugate addition reactions. Aliphatic aldehydes were tolerated (**21**-**24**) when performed under a $CO_2$ atmosphere, while various aldol condensation products were observed under $N_2$ atmosphere, highlighting the importance of the $CO_2$-mediated cyanohydrin formation conditions. For example, when 3-phenylpropionaldehyde (**22**) was subjected to the reaction conditions under $N_2$ atmosphere, a complicated reaction mixture was observed due to aldol-reaction related byproducts. Furthermore, the cyanation reaction of sterically hindered free alcohol was achieved (**23**), which would otherwise not be straightforward by classical means.[18] Despite the reduced reactivity of ketones,[11] both α-keto acids (**27**-**28**) and aliphatic ketones (**25**-**26**) were smoothly transformed into cyanohydrins in good to excellent yield, with no hemiketal[18] or aldol-reaction related by-products formation.




**Scheme 2.** Substrate scope of carbon dioxide mediated cyanohydrin synthesis of aromatic and aliphatic aldehydes and ketones. Cyanohydrin formation: carbonyl (1 mmol), KCN (2 eq), EtOH (0.5 M) and $CO_2$ (1 atm) was stirred at rt for 18 h. Cyano xanthate formation: aldehyde (1 mmol), KCN (5 eq), $CS_2$ (10 eq), MeI (5 eq) and MeCN (0.5 M) was stirred at 0 °C for 4 h, then rt for 2 h.[a] Reaction performed on a 100 mmol scale using KCN (1.2 eq). [b] Reaction performed on a 500 mmol scale using KCN (1.2 eq). [c] KCN (3 eq). [d] Performed under a $CO_2$ atmosphere. [e] Performed under a $N_2$ atmosphere.

The cyanohydrin formation reaction was feasible in the presence of $CS_2$ as a $CO_2$ surrogate. In this case, we expected that the formation of xanthate would render a synthetic platform to diversify the product. Both aryl and aliphatic aldehydes were converted into the corresponding cyano methyl xanthates in excellent yields under optimized conditions (**29**-**30**, See Tables S15-S17 for more details), demonstrating, to the best of our knowledge, the first example of an α-aryl cyano xanthate. We observed that the presence of $CO_2$ is critical for the successful xanthate formation reaction of aromatic aldehydes with $CS_2$. We presumed that the carbonate and dithiocarbonate exchange equilibrium would afford desired products after methylation reaction. In contrast, aliphatic aldehyde was smoothly transformed to the corresponding α-cyano xanthate (**30**) under nitrogen atmosphere.

With these results in our hands, we sought the developed cyanohydrin synthesis and xanthate formation reaction can offer two distinct modes of intuitive homologation strategy: 1) CHO homologation by preserving the hydroxy group of cyanohydrin, and 2) $CH_2$ homologation combined with Barton-McCombie deoxygenation conditions.[28] These would enable selective elongation via "expanded" Kiliani-Fischer synthesis, which has been restricted to CHO-elongation of carbohydrate-based aldehydes. Additionally, to the best of knowledge, previously reported cyanohydrin formation and elongation sequences are limited to aliphatic aldehyde substrates, which can not undergo aldol and benzoin reactions.[29] After extensive optimization, we confirmed that the cyanohydrin synthesis is highly scalable up to 500 mmol scale (**1** and **22**, Scheme 2). The obtained cyanohydrin was smoothly transformed into the corresponding TBDMS protected cyanohydrin, **31**, (CHO elongation, 91%, 2 steps), and alkyl nitrile, **35**, ($CH_2$ elongation, 85%, 2 steps) after protection and the reductive deoxygenation reaction, respectively. Each elongation sequence was further iterated to generate α-hydroxy aldehyde for CHO elongation and $CH_2$ elongation to afford 1,2-diol, **32**, in 71% yield (3 steps) and β-hydroxy nitrile **34** in excellent isolated yield (93%). Alkyl nitrile **35**, the $CH_2$ elongation product, was further functionalized to TBDMS-protected cyanohydrin, **36**, in 75% yield (3 steps), and two-carbon elongated linear nitrile, **38**, in high isolated yield (92%, Scheme 3). Combinations of CHO and $CH_2$ elongation display a selective iterative 3-step sequence homologation, providing straightforward retrosynthetic pathways for linear hydrocarbons with functional groups and variety of polyketide-like products under practical and simple reaction conditions enabled by $CO_2$.

To shed some lights on the reaction mechanism, we attempted to isolate the carbonate species from the $CO_2$-mediated cyanohydrin formation reaction. We obtained the Cbz (carboxylbenzyl) protected cyanohydrin, **39** (Scheme 4A), whereas preformed cyanohydrin (**22**) afforded no product under $CO_2$ atmosphere (Scheme 4B), suggesting in-situ cyanoformate and cyanohydrin formations may be responsible for the successful $CO_2$ mediated reaction. It is noteworthy here that our protocol demonstrates the synthesis of Cbz protected cyanohydrin from carbon dioxide, without the need for reactive reagents such as benzyl cyanoformate or chloroformates.[30]

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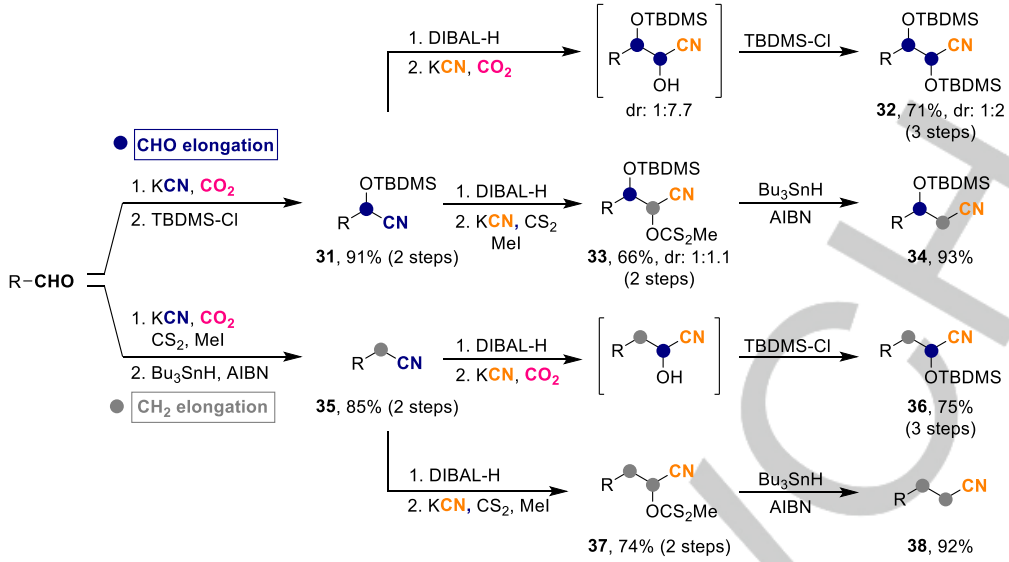
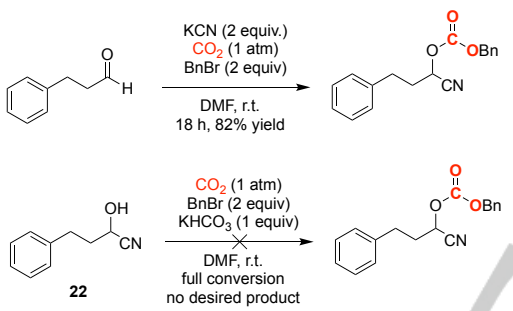



**Scheme 3.** Kiliani-Fischer homologation and iterative elongation by $CO_2$- and $CS_2$-mediated cyanation with KCN (R = 4-F-$C_6H_4$)




**Scheme 4.** Attempts to access Cbz-protected cyanohydrin from $CO_2$ and (A) an aldehyde with KCN, and (B) with a preformed cyanohydrin (**22**).

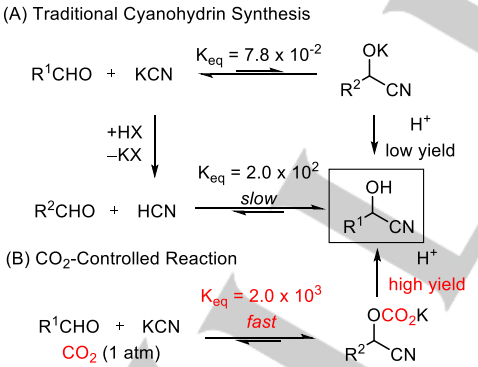



**Figure 2.** (A) Reported equilibrium constants for traditional cyanohydrin synthesis with HCN[31] and (B) $CO_2$-controlled reactions with KCN and ($R^1$ = 4-F-$C_6H_4$, $R^2$ = $C_6H_5$, all reactions were in ethanol at room temperature)

In conclusion, we have developed a synthetic method to access cyanohydrins under practical conditions, which enabled a general method for homologation sequences using a convenient cyanide source, potassium cyanide, mediated by carbon dioxide. In the absence of $CO_2$, it was found that aldehydes were prone to form byproducts related to benzoin reaction and aldol condensation reactions due to the nucleophilic and basic cyanide. These side reactions were prohibited by the action of $CO_2$, acting as a temporary protecting group, thus providing the broad substrate scope for cyanohydrins, xanthates, and iterative homologation reactions. A brief thermodynamic analysis of the cyanohydrin synthesis confirms that the desired reaction pathways is not viable with KCN under conventional reaction conditions (Figure 2A). The obtained equilibrium constant with KCN and $CO_2$ is an order of magnitude greater than the reported value with HCN (2.0 x $10^2$) with HCN.[31] We therefore believe that $CO_2$ is not only changing the polarity of the reaction medium as an additive, but also affecting the equilibrium by forming stable adducts with $CO_2$ while acting as a general catalyst. This can be a general method in organic synthesis considering many reactions are performed with nucleophilic reagents undergoing anionic or negatively charged intermediates and transition states. The use of $CO_2$ is highly practical by simplifying work-up procedures without any remaining protecting groups or reagents after the removal of $CO_2$, highlighted by large scale reactions. Further studies in detailed mechanisms of $CO_2$-mediated cyanohydrin synthesis are under investigation.

## Acknowledgements

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**Keywords:** carbon dioxide • cyanohydrins • homologation • xanthate • elongation

[1] E. V. Anslyn, D. A. Dougherty Modern Physical Organic Chemistry, University Science, **2005**

[2] Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, *6*, 5933.

[3] (a) T. Sakakura, J. C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365-2387. (b) J. Hong, M. Li, J. Zhang, B. Sun, F. Mo, *ChemSusChem* **2019**, *12*, 6-39. (c) A. Tortajada, F. Juliá-Hernández, M. Börjesson, T. Moragas, R. Martin, *Angew. Chem. Int. Ed.* **2018**, *57*, 15948-15982.

[4] (a) W. Schilling, S. Das, *Tetrahedron Lett.* **2018**, *59*, 3821-3828. (b) Y. Yang, J.-W. Lee, *Chem. Sci.* **2019**, *10*, 3905-3926. (c) A. Tortajada, F.

Julia-Hernandez, M. Borjesson, T. Moragas, R. Martin, *Angew. Chem., Int. Ed.,* **2018**, *57*, 15948. (d) M. Börjesson, T. Moragas, D. Gallego, R. Martin, *ACS Catal*., **2016**, *6*, 6739.

[5] (a) F. Juliá-Hernández, T. Moragas, J. Cornella, R. Martin, *Nature* **2017**, *545*, 84-88. (b) J. Luo, S. Preciado, P. Xie, I. Larrosa, *Chem. Eur. J.* **2016**, *22*, 6798-6802. (c) T. Mita, J. Chen, M. Sugawara, Y. Sato, *Angew. Chem. Int. Ed.* **2011**, *50*, 1393-1396. (d) G. A. Olah, B. Török, J. P. Joschek, I. Bucsi, *J. Am. Chem. Soc.* **2002**, *124*, 11379-11391. (e) G. Destro, O. Loreau, E. Marcon, F. Taran, T. Cantat, D. Audisio, *J. Am. Chem. Soc.* **2019**, *141*, 780-784. (f) G. Fiorani, W. Guo, A. W. Kleij, *Green Chem* **2015**, *17*, 1375.1389. (g) Q.-W. Song, Z.-H. Zhou, L.-N. He, *Green Chem* **2017**, *19*, 3707.

[6] (a) J. Ye, I. Kalvet, F. Schoenebeck, T. Rovis, *Nat. Chem.* **2018**, *10*, 1037–1041. (b) M. Kapoor, P. Chand-Thakuri, M. C. Young, *J. Am. Chem. Soc.* **2019**, *141*, 7980-7989.

[7] G. Pupo, R. Properzi, B. List, *Angew. Chem. Int. Ed.* **2016**, *55*, 6099-6102.

[8] D. Riemer, B. Mandaviya, W. Schilling, A. C. Götz, T. Kühl, M. Finger, S. Das, *ACS Catal*. **2018**, *8*, 3030-3034.

[9] T. Roy, M. J. Kim, Y. Yang, S. Kim, G. Kang, X. Ren, A. Kadziola, H. Y. Lee, M. H. Baik, J.-W. Lee, *ACS Catal.* **2019**, *9*, 6006-6011.

[10] F. L. Winkler, *Ann. Chem.* **1832**, *4*, 242-247.

[11] M. North, D. L. Usanov, C. Young, *Chem. Rev.* **2008**, *108*, 5146–5226.

[12] N. Kurono, T. Ohkuma, *ACS Catal.* **2016**, *6*, 989-1023.

[13] P. Bracco, H. Busch, J. Von Langermann, U. Hanefeld, *Org. Biomol. Chem.* **2016**, *14*, 6375-6389.

[14] (a) F. Effenberger, U. Stelzer, *Angew. Chem.* **1991**, *103*, 866-867. (b) J. Scharfbier, H. Hazrati, E. Irran, M. Oestreich, *Org. Lett.* **2017**, *19*, 6562-6565. (c) F. Effenberger, S. Gaupp, *Tetrahedron Asymme.* **1999**, *10*, 1765-1775. (d) F. Effenberger, A. Kremser, U. Stelzer, *Tetrahedron Asymm.* **1996**, *7*, 607-618. (e) M. Remli, R. Guedj, *J. Fluor. Chem.* **1983**, *22*, 493-497. (f) A. S. Donslund, K. T. Neumann, N. P. Corneliussen, E. K. Grove, D. Herbstritt, K. Daasbjerg, T. Skrydstrup, *Chem. Eur. J.* **2019**, *25*, 9856-9860.

[15] (a) W. Lidy, W. Sundermeyer, *Chem. Ber.* **1973**, *106*, 587-593. (b) D. A. Evans, L. K. Truesdale, G. L. Carroll, *Chem. Commun.* **1973**, 55-56.

[16] C. S. Marvel, N. O. Brace, F. A. Miller, A. R. Johnson, *J. Am. Chem. Soc.* **1949**, *71*, 34-36.

[17] Z. Zhang, H. Y. Bae, J. Guin, C. Rabalakos, M. Van Gemmeren, M. Leutzsch, M. Klussmann, B. List, *Nat. Commun.* **2016**, *7*, 12478.

[18] (a) G. Zhang, L. Fu, P. Chen, J. Zou, G. Liu, *Org. Lett.* **2019**, *21*, 5015-5020. (b) K. Mai, G. Patil, *J. Org. Chem.* **1986**, *51*, 3545-3548.

[19] J. W. Baker, M. L. Hemming, *J. Chem. Soc.* **1942**, 191-198.

[20] E. V. Anslyn, D. A. Dougherty Modern Physical Organic Chemistry; University Science, **2005**; pp 537-625.

[21] W. Nagata, M. Yoshioka, *Tetrahedron Lett.* **1966**, *7*, 1913-1918.

[22] K. C. Nicolaou, G. Vassilikogiannakis, R. Kranich, P. S. Baran, Y. L. Zhong, S. Natarajan, *Org. Lett.* **2000**, *2*, 1895-1898.

[23] C. S. Hudson, *Adv. Carbohydr. Chem.* **1945**, *1*, 1-36.

[24] M. Juhl, J.-W. Lee, *Angew. Chem. Int. Ed.* **2018**, *57*, 12318-12322.

[25] (a) C. Hering, J. Von Langermann, A. Schulz, *Angew. Chem. Int. Ed.* **2014**, *53*, 8282-8284. (b) L. J. Murphy, K. N. Robertson, S. G. Harroun, C. L. Brosseau, U. Werner-Zwanziger, J. Moilanen, H. M. Tuononen, J. A. C. Clyburne, *Science* **2014**, *344*, 75-78.

[26] E. Palombo, G. Audran, H. Monti, *Synlett* **2005**, *6*, 2104-2106.

[27] D. T. Mowry, *Chem. Rev*. **1948**, *42*, 189-283.

[28] (a) W. Hartwig, *Tetrahedron* **1983**, *39*, 2609-2645. (b) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413-1432.

[29] Z. Györgydeák, I. F. Pelyvás Monosaccharide Sugars - Chemical Synthesis by Chain Elongation, Degradation, and Epimerization, Academic: San Diego, **1998**.

[30] K. Iwanami, Y. Hinakubo, T. Oriyama, *Tetrahedron Lett.* **2005**, *46*, 5881-5883.

[31] A. Lapworth, R. H. F. Manske, *J. Chem. Soc.* **1928**, 2533– 2549.

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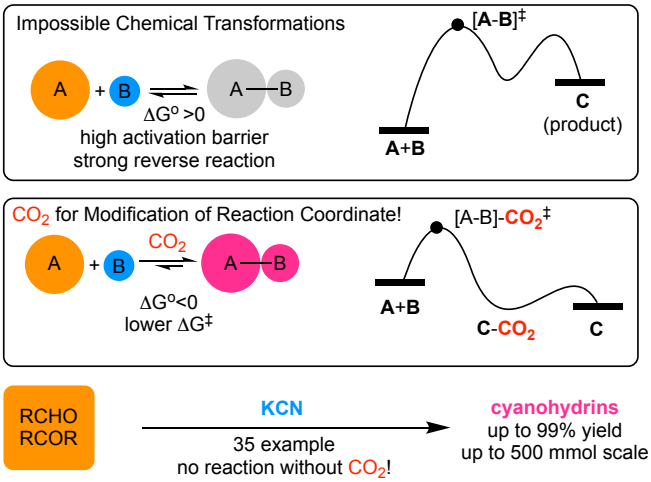


Carbon-dioxide promotes cyanohydrins synthesis, enabling facile and iterative homologation reactions for organic synthesis. This traceless, practical and atom-efficient cyanohydrin synthesis shows a broad substrate scope with high isolated yields of synthetically versatile cyanohydrins. The use of $CO_2$ can be productive in chemical reactions undergoing anionic intermediates and negatively charged transitions states, which can be stabilized by Lewis-acidic $CO_2$.

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