CO_2-Enabled Cyanohydrin Synthesis and Facile Homologation Reactions

Martin Juhl[†], Allan R. Petersen[†], Ji-Woong Lee*[,†]

[†]Department of Chemistry, Nano-Science Center, University of Copenhagen, Universitetsparken 5, Copenhagen Ø, 2100, Denmark

KEYWORDS: Carbon Dioxide, Cyanohydrin, Xanthate, Homologation

ABSTRACT: Thermodynamic and kinetic control of a chemical process is the key to access desired products and states. Changes are made when 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 direct reaction pathways in order to selectively afford desired products in high reaction rates while avoiding the formation of byproducts. The utility of CO_2-mediated selective cyanohydrin synthesis was further showcased by broadening Kiliani-Fischer synthesis to offer an easy access to variety of polyols, cyanohydrins, linear alkylnitriles, by simply starting from alkyl- and arylaldehydes, KCN and 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 presence and the absence of CO_2 – a mild Lewis and potentially Brønsted acid. Here we demonstrate our strategy by accelerating an organic reaction; nucleophilic 1,2-addition of a carbon nucleophile to carbonyl compounds, namely cyanohydrin formation reaction promoted by CO_2. Facile homologation of aldehydes with cyanide was realized expanding the scope beyond Killiani-Fischer synthesis, under practical reaction conditions, accessing variety of compounds in a modular fashion.

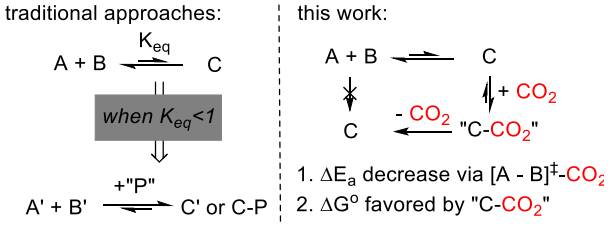
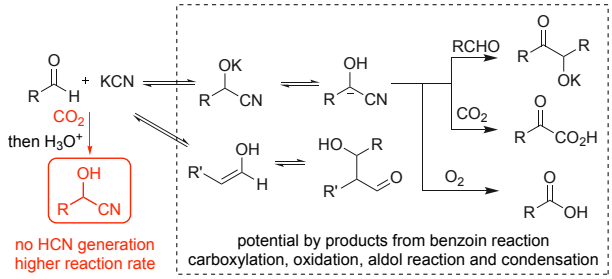


Figure 1. A comparison of traditional reaction optimization and our CO_2-approach. (P = catalysts, protecting groups or trapping reagents)

Carbon dioxide is intrinsically stable molecule,[2-3] however, it can readily and reversibility 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, reported in 1832 by Winkler using HCN as a cyanide source.[10] Despite the high utility of cyanohydrins in organic synthesis[11-14] the use of HCN may reduce its application potential due to its volatile nature and health risks. Recent activities in cyanohydrin synthesis are mainly performed by using TMSCN[15] and cyanoformate[16] as an HCN surrogate.[11,12,17] These reagents suffer from poor atom economy when un-protected cyanohydrins are desired. Furthermore, the cyanation reactions with *in-situ* generated HCN (from mixture of TMSCN and an alcohol) are limited by the instability of the cyanide sources thereby limiting the solvent compatibility. [11,18]

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 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, which



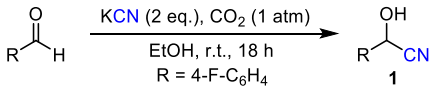
Scheme 1. Cyanohydrin synthesis enabled by CO_2/KCN and side reaction pathways.

requires sophisticated cyanide sources and reagents. For example, high selectivity towards cyanohydrin formation was realized assisted by an activating 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 neutral conditions led us to investigate the potential utility of CO_2 in cyanohydrin synthesis with alkaline metal cyanides. Under mild conditions, CO_2 can generate slightly acidic medium thus enabling catalysis, while exhibiting Lewis acidic character at the central carbon for trapping and stabilizing anionic species. However, another challenge lays on the side reactions: benzoin- and self-aldol reactions from KCN and aldehydes, generating numerous byproducts (Scheme 1). Based on our previous work, we sought that the use of CO_2 in principle provide a practical method by minimzing side products, while overcoming the limit of Kiliani-Fischer synthesis beyond carbohydrate modification via selective cyanohydrin synthesis.[23]

We have recently shown the applicability cyanohydrins as a nucleophile via an umpolung strategy (Scheme 1, α-keto acid synthesis).[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 ($k = 2.50 \times 10^{-3}$). This is approximately 10^5-folds rate acceleration compared to the reported values,[19] which is surprising considering that the reaction requires the solubilization of KCN in the organic solvent. We verified that the solubility of KCN was increased in the presence of CO_2 (Figure S6), which can be ascribed to the formation of cyanoformate in solution liberating solubilized cyanide nucleophiles.[25] Therefore, we performed various control experiments as summarized in Table 1. Under CO_2 atmosphere (1 atm), full conversion of the starting material (**1a**) was observed to the desired cyanohydrin affording 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), indicating the reaction reached fast equilibrium in favor of starting materials. More importantly, in situ generated HCN gave inferior result, (entry 3, 21% yield), while quantitative yield was obtained with KCN/CO_2 combination within 30 minutes (entry 4, 91%). Variety of solvents were found to be compatible to induce desired product (i.e. ethanol, heptane, acetonitrile and water, see supporting information for full optimization, Table S1-13) showing the generality of the use of CO_2 to accelerate cyanohydrin synthesis. The solubility of cyanide is important – a soluble cyanide source, ammonium cyanide, showed good conversion to the product however, the reaction was not efficient under inert N_2 atmosphere (entries 12 and 13). Therefore, we concluded that CO_2 is not innocent in this reaction, and it was evident that the reaction can be promoted by carbon dioxide whereas a strong acid (e.g. HCl) afforded only low yield of the product since HCN (a "slower" nucleophile) generation is favored (entry 14). The use of acetic acid[26] showed compatible result (entry 15) confirming that weak acid can indeed catalyze the reaction, by prohibiting the complete protonation of KCN.

Table 1. Optimizing CO_2 Mediated Cyanation



Entry	Deviation from standard reaction conditions	Yield[b]
1	None	99% (97%)[c]
2	No CO_2 (under N_2)	7%
3	HCN (2 equiv) instead of KCN	21%
4	30 min of reaction time	91%
5	H_2O as a solvent	95%
6	*n*-heptane as a solvent	87%
7	toluene as a solvent	9%
8	DCM as a solvent	22%
9	DCM as a solvent + DBU (1 eq)	97%
11	NaCN, 30 min	57%
12	NEt_4CN, 30 min	97%
13	NEt_4CN, 30 min, under N_2	33%
14	aq. 5M HCl (4 eq.) instead of CO_2	24%
15	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. [c]Isolated yield.

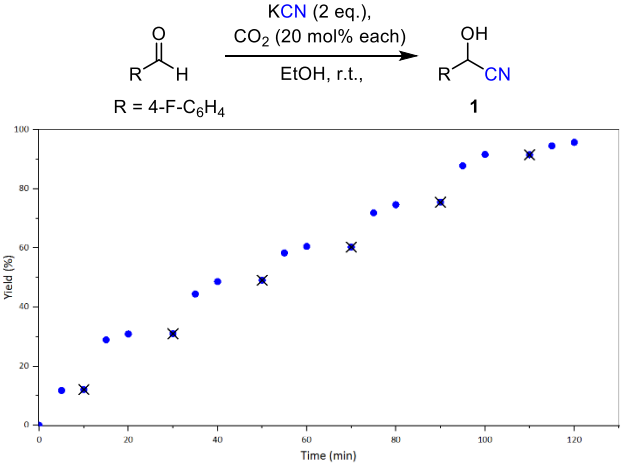
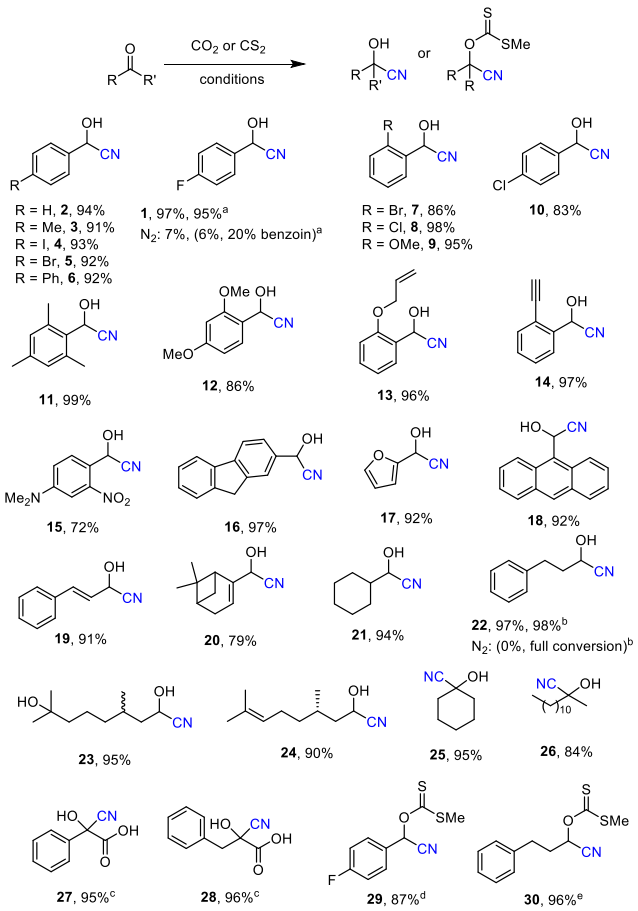


Figure 2. Cyanohydrin formation using stoichiometric amounts of CO_2. After 10 min was added CO_2 (20 mol%) every 20 min. Cross (X) marks the addition of catalytic amounts of CO_2 (20 mol%).

The role of CO_2 in the cyanohydrin synthesis was further verified by adding catalytic amounts of CO_2 (20 mol%) to a reaction mixture repeatedly (Figure 2). 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.

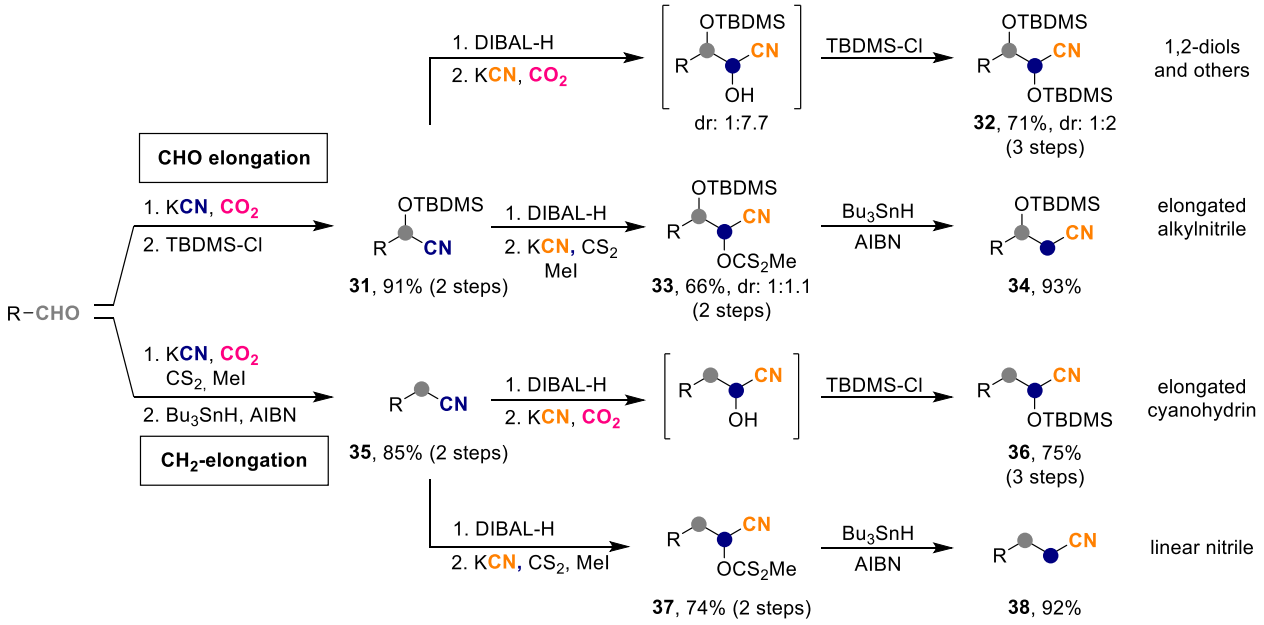
Having demonstrated the feasibility of the CO_2 promoted cyanohydrin formation, we explored the scope of the reaction with respect to both aryl and alkyl aldehydes and ketones (Scheme 2). A variety of aryl aldehydes was tested and provided the corresponding cyanohydrin in excellent yields regardless their substitution in terms of electron donating and withdrawing 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 by-product derived from 1,4-conjugate addition reactions. Aliphatic aldehydes were tolerated (**20**-**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. The cyanohydrin formation reaction was operative in the presence of CS_2 as a surrogate to carbon dioxide. 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 xanthate in excellent yields under optimized conditions (**29**-**30**, See Tables S15-S17 for more detail), demonstrating, to the best of our knowledge, the first example of α-aryl cyano xanthate. The xanthate formation reaction of aryl aldehydes was also facilitate under carbon dioxide atmosphere, suggesting cyanohydrin formation promoted by CO_2. We presumed that the carbonate and dithiocarbonate exchange equilibrium would afford desired products after methylation reaction with MeI.



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.

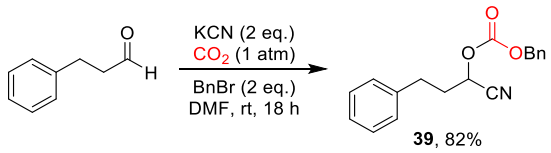
Scheme 2. Carbon dioxide Mediated Cyanohydrin Synthesis



Scheme 3. "Expanded" Kiliani-Fischer Homologation and Elongation by CO_2- and CS_2-mediated Cyanation. (R = 4-F-C_6H_4)

With these results in our hands, we sought the developed cyanohydrin synthesis demonstrates two different modes for facile and intuitive homologation strategy: 1) CHO homologation by preserving the hydroxy group of cyanohydrin, and 2) CH_2 homologation using Barton-McCombie reduction conditions.[28] These would be allowing for 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] Under optimized reaction conditions, the obtained cyanohydrins was smoothly transformed into the corresponding TBDMS protected cyanohydrin, **31**, (91%, 2 steps), and alkyl nitrile, **35**, (85%, 2 steps) after protection and reductive deoxygenation reaction, respectively. Each elongation sequence was further repeated 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 93% yield. The alkyl nitrile was further functionalized to demonstrate the possibility of CHO elongation and CH_2 elongation to generate elongated TBDMS-protected cyanohydrin, **36**, in 75% yield (3 steps), and two-carbon elongated linear nitrile, **38**, in 92% isolated yield (Scheme 3). All combination of CHO and CH_2 elongation displays selective homologation in 3-steps sequence providing a variety of products under practical and simple reaction conditions enabled by CO_2 atmosphere.

To shed some lights on the reaction mechanism, we attempted to isolate the carbonate species from the CO_2-mediated cyanohydrin formation reaction (Scheme 4). Fortunately, we obtained the Cbz (carboxylbenzyl) protected cyanohydrin, **39**, in 82% yield by using benzyl bromide under CO_2 atmosphere, suggesting the formation of potassium cyanohydrin carbonate. 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]



Scheme 4. Synthesis of Cbz Protected Cyanohydrin with CO_2

In conclusion, we have developed a synthetic method to access cyanohydrins under practical conditions, which enabled a general method for homologation sequences using potassium cyanide and carbon dioxide. In general, it was found that aldehydes were prone to predominantly form byproducts related to benzoin reaction and aldol condensation reactions in the absence of CO_2. These side reactions were prohibited by the action of CO_2, acting as a temporary protecting group and providing a broad substrate scope of cyanohydrin and xanthates.

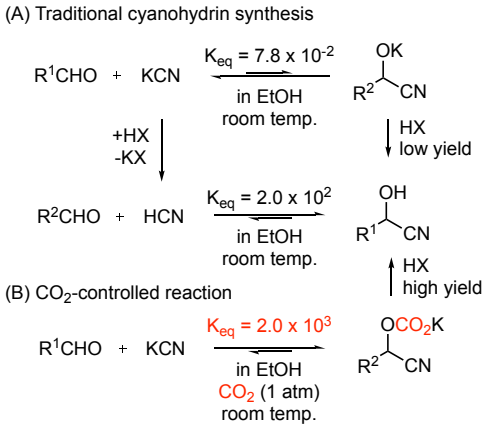


Figure 3. (A) Traditional cyanohydrin synthesis and reported equilbrium constants (at room tempearture) and (B) A suggested reaction mechanism of CO_2-controlled reaction (R^1 = 4-F-C_6H_4, R^2 = C_6H_5)

Thermodynamic analysis of the cyanohydrin synthesis revealed that the desired reaction pathways is not viable with KCN under conventional reaction conditions (Figure 3). The reported equilibrium constant of cyanohydrin synthesis with HCN is in a stark difference with the obtained values in the current study with KCN/CO_2. We therefore believe that CO_2 is not only changing the polarity of the reaction medium, facilitating the reaction, but also affecting the equilibrium of the reaction while forming stable adducts with CO_2. A strong acid is not as efficient as CO_2 since it generates HCN, which shows a slower reaction rate albeit the favored equilibrium to the right side (Figure 3A). 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. Further investigations in other types of organic reactions and asymmetric cyanohydrin synthesis promoted by CO_2 are underway.

ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR, optimization tables and mechanistic studies.

AUTHOR INFORMATION

Corresponding Author

Ji-Woong Lee: jiwoong.lee@chem.ku.dk

ORCID

Martin Juhl: 0000-0001-5395-9627
Allan R. Petersen: 0000-0002-6381-8083
Ji-Woong Lee: 0000-0001-6177-4569

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

Department of Chemistry, University of Copenhagen

The Novo Nordisk Fonden (Grant No. NNF17OC0027598)

The Villum Fonden (00019062)

ACKNOWLEDGMENT

The generous support of the Department of Chemistry, University of Copenhagen is gratefully acknowledged.

REFERENCES

(1) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science, 2005; pp 65-143

(2) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. Using Carbon Dioxide as a Building Block in Organic Synthesis. *Nat. Commun.* **2015**, *6*, 5933.

(3) (a) Sakakura, T.; Choi, J. C.; Yasuda, H. Transformation of Carbon Dioxide. *Chem. Rev.* **2007**, *107*, 2365–2387. (b) Hong, J.; Li, M.; Zhang, J.; Sun, B.; Mo, F. C−H Bond Carboxylation with Carbon Dioxide. *ChemSusChem* **2019**, *12*, 6–39. (c) Tortajada, A.; Juliá-Hernández, F.; Börjesson, M.; Moragas, T.; Martin, R. Transition-Metal-Catalyzed Carboxylation Reactions with Carbon Dioxide. *Angew. Chem. Int. Ed.* **2018**, *57*, 15948–15982.

(4) Yang, Y.; Lee, J.-W. Toward Ideal Carbon Dioxide Functionalization. *Chem. Sci.* **2019**, *10*, 3905–3926.

(5) (a) Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. Remote Carboxylation of Halogenated Aliphatic Hydrocarbons with Carbon Dioxide. *Nature* **2017**, *545*, 84–88. (b) Luo, J.; Preciado, S.; Xie, P.; Larrosa, I. Carboxylation of Phenols with CO_2 at Atmospheric Pressure. *Chem. Eur. J.* **2016**, *22*, 6798–6802. (c) Mita, T.; Chen, J.; Sugawara, M.; Sato, Y. One-Pot Synthesis of α-Amino Acids from Imines through CO_2 Incorporation: An Alternative Method for Strecker Synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 1393–1396. (d) Olah, G. A.; Török, B.; Joschek, J. P.; Bucsi, I.; Esteves, P. M.; Rasul, G.; Prakash, G. K. S. Efficient Chemoselective Carboxylation of Aromatics to Arylcarboxylic Acids with a Superelectrophilically Activated Carbon Dioxide-Al_2Cl_6/Al System. *J. Am. Chem. Soc.* **2002**, *124*, 11379–11391. (e) Destro, G.; Loreau, O.; Marcon, E.; Taran, F.; Cantat, T.; Audisio, D. Dynamic Carbon Isotope Exchange of Pharmaceuticals with Labeled CO_2. *J. Am. Chem. Soc.* **2019**, *141,* 780–784.

(6) (a) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. Direct α-Alkylation of Primary Aliphatic Amines Enabled by CO_2 and Electrostatics. *Nat. Chem.* **2018**, *10*, 1037–1041. (b) Kapoor, M.; Chand-Thakuri, P.; Young, M. C. Carbon Dioxide-Mediated C(sp^2)-H Arylation of Primary and Secondary Benzylamines. *J. Am. Chem. Soc.* **2019**, *141*, 7980–7989.

(7) Pupo, G.; Properzi, R.; List, B. Asymmetric Catalysis with CO_2: The Direct α-Allylation of Ketones. *Angew. Chem. Int. Ed.* **2016**, *55*, 6099–6102.

(8) Riemer, D.; Mandaviya, B.; Schilling, W.; Götz, A. C.; Kühl, T.; Finger, M.; Das, S. CO_2-Catalyzed Oxidation of Benzylic and Allylic Alcohols with DMSO. *ACS Catal.* **2018**, *8*, 3030–3034.

(9) Roy, T.; Kim, M. J.; Yang, Y.; Kim, S.; Kang, G.; Ren, X.; Kadziola, A.; Lee, H. Y.; Baik, M. H.; Lee, J.-W. Carbon Dioxide-Catalyzed Stereoselective Cyanation Reaction. *ACS Catal.* **2019**, *9*, 6006–6011.

(10) Winkler, F. L. Ueber Einige Bestandtheile Der Bittermandeln. *Liebigs Ann. Chem* **1832**, *4*, 242–247.

(11) North, M.; Usanov, D. L.; Young, C. Lewis Acid Catalyzed Asymmetric Cyanohydrin Synthesis. *Chem. Rev.* **2008**, *108*, 5146–5226.

(12) Kurono, N.; Ohkuma, T. Catalytic Asymmetric Cyanation Reactions. *ACS Catal.* **2016**, *6*, 989–1023.

(13) Bracco, P.; Busch, H.; Von Langermann, J.; Hanefeld, U. Enantioselective Synthesis of Cyanohydrins Catalysed by Hydroxynitrile Lyases-a Review. *Org. Biomol. Chem.* **2016**, *14*, 6375–6389.

(14) (a) Effenberger, F.; Stelzer, U. Darstellung Und Stereoselektive Reaktionen von (R)-α-Sulfonyloxynitrilen. *Angew. Chem.* **1991**, *103*, 866–867. (b) Scharfbier, J.; Hazrati, H.; Irran, E.; Oestreich, M. Copper-Catalyzed Substitution of α-Triflyloxy Nitriles and Esters with Silicon Nucleophiles under Inversion of the Configuration. *Org. Lett.* **2017**, *19*, 6562–6565. (c) Effenberger, F.; Gaupp, S. Stereoselective Substitution of (R)-2-(Sulfonyloxy) Nitriles with Sulfur Nucleophiles. *Tetrahedron Asymmetry* **1999**, *10*, 1765–1775. (d) Effenberger, F.; Kremser, A.; Stelzer, U. A Convenient Synthesis of (S)-2-Azidonitriles, (S)-2-Aminonitriles and (S)-1,2-Diamines. *Tetrahedron Asymm.* **1996**, *7*, 607–618. (e) Remli, M.; Guedj, R. Some New Chemical Properties of Fluorohydrins. *J. Fluor. Chem.* **1983**, *22*, 493–497. (f) Donslund, A. S.; Neumann, K. T.; Corneliussen, N. P.; Grove, E. K.; Herbstritt, D.; Daasbjerg, K.; Skrydstrup, T. Access to β-Ketonitriles through Nickel-Catalyzed Carbonylative Coupling of α-Bromonitriles with Alkylzinc Reagents. *Chem. Eur. J.* **2019**, *25*, 9856–9860.

(15) (a) Lidy, W.; Sundermeyer, W. Spaltungsreaktionen Des Trimethylsilylcyanids, Eine Neue Darstellungsmethode Für O-(Trimethylsilyl)Cyanhydrine. *Chem. Ber.* **1973**, *106*, 587–593. (b) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. Cyanosilylation of Aldehydes and Ketones. A Convenient Route to Cyanohydrin Derivatives. *Chem. Commun.* **1973**, 55–56.

(16) Marvel, C. S.; Brace, N. O.; Miller, F. A.; Johnson, A. R. Benzoyl Cyanide Dimer and the Addition of Benzoyl Cyanide to Aromatic Aldehydes. *J. Am. Chem. Soc.* **1949**, *71*, 34–36.

(17) Zhang, Z.; Bae, H. Y.; Guin, J.; Rabalakos, C.; Van Gemmeren, M.; Leutzsch, M.; Klussmann, M.; List, B. Asymmetric Counteranion-Directed Lewis Acid Organocatalysis for the Scalable Cyanosilylation of Aldehydes. *Nat. Commun.* **2016**, *7*,

12478.

(18) (a) Zhang, G.; Fu, L.; Chen, P.; Zou, J.; Liu, G. Proton-Coupled Electron Transfer Enables Tandem Radical Relay for Asymmetric Copper-Catalyzed Phosphinoylcyanation of Styrenes. *Org. Lett.* **2019**, *21*, 5015–5020. (b) Mai, K.; Patil, G. Alkylsilyl Cyanides as Silylating Agents. *J. Org. Chem.* **1986**, *51*, 3545–3548.

(19) Baker, J. W.; Hemming, M. L. The Aldehydecyanohydrin Reaction. *J. Chem. Soc.* **1942**, 191–198.

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

(21) Nagata, W.; Yoshioka, M. Alkylaluminum Cyanides as Potent Reagents for Hydrocyanation. *Tetrahedron Lett.* **1966**, *7*, 1913–1918.

(22) Nicolaou, K. C.; Vassilikogiannakis, G.; Kranich, R.; Baran, P. S.; Zhong, Y. L.; Natarajan, S. New Synthetic Technology for the Mild and Selective One-Carbon Homologation of Hindered Aldehydes in the Presence of Ketones. *Org. Lett.* **2000**, *2*, 1895–1898.

(23) Hudson, C. S. The Fischer Cyanohydrin Synthesis and the Configurations of Higher-Carbon Sugars and Alcohols. *Adv. Carbohydr. Chem.* **1945**, *1*, 1–36.

(24) Juhl, M.; Lee, J.-W. Umpolung Reactivity of Aldehydes toward Carbon Dioxide. *Angew. Chemie - Int. Ed.* **2018**, *57*, 12318–12322.

(25) (a) Hering, C.; Von Langermann, J.; Schulz, A. The Elusive Cyanoformate: an Unusual Cyanide Shuttle. *Angew. Chemie - Int. Ed.* **2014**, *53*, 8282–8284. (b) Murphy, L. J.; Robertson, K. N.; Harroun, S. G.; Brosseau, C. L.; Werner-Zwanziger, U.; Moilanen, J.; Tuononen, H. M.; Clyburne, J. A. C. A Simple Complex on the Verge of Breakdown: Isolation of the Elusive Cyanoformate Ion. *Science* **2014**, *344*, 75–78.

(26) Palombo, E.; Audran, G.; Monti, H. Enantioselective Synthesis of (+)-Ricciocarpin A Using an Auxiliary Hydroxyl Group and a Diastereofacial Selectivity Based Methodology. *Synlett* **2005**, *6*, 2104–2106.

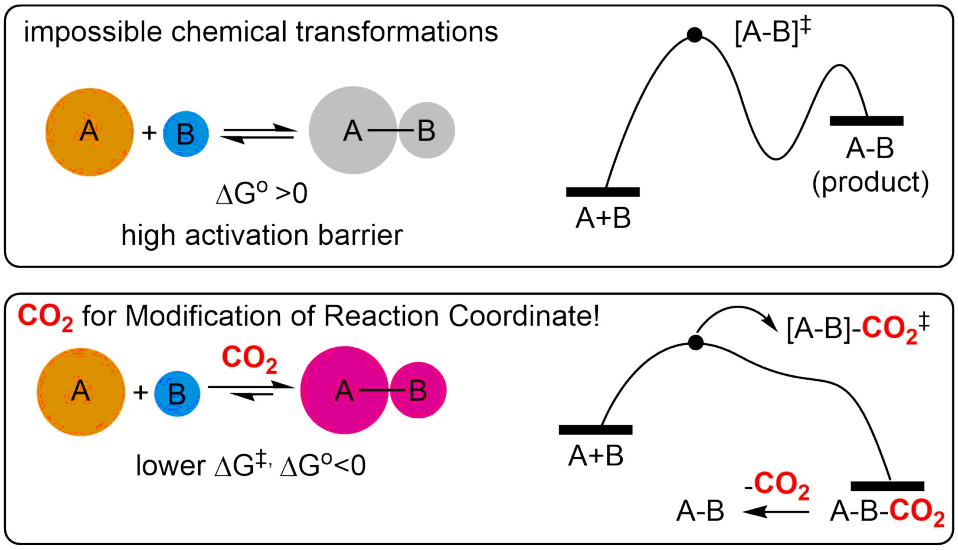
(27) Mowry, D. T. The Preparation of Nitriles. *Chem. Rev.* **1948**, *42*, 189–283.

(28) (a) Hartwig, W. Modern Methods for the Radical Deoxygenation of Alcohols. *Tetrahedron* **1983**, *39*, 2609–2645. (b) Crich, D.; Quintero, L. Radical Chemistry Associated with the Thiocarbonyl Group. *Chem. Rev.* **1989**, *89*, 1413–1432.

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

(30) Iwanami, K.; Hinakubo, Y.; Oriyama, T. Catalyst-Free DMSO-Promoted Synthesis of Cyanohydrin Carbonates from Aldehydes. *Tetrahedron Lett.* **2005**, *46*, 5881–5883.

(31) Lapworth, A.; Manske, R. H. F. The Conditions Determining the Thermodynamic Stability of Cyanohydrins of Carbonyl Compounds. Part I. Some Effects of (a) Substitution in Aromatic Aldehydes and (b) Ring Formation. *J. Chem. Soc.* **1928**, 2533–2549.


impossible chemical transformations
A
+
B
A—B
ΔG° >0
high activation barrier
[A-B]‡
A-B
(product)
A+B
CO2 for Modification of Reaction Coordinate!
A
+
B
CO2
A—B
lower ΔG‡, ΔG°<0
[A-B]-CO2‡
A+B
-CO2
A-B
A-B-CO2