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Enantioselective α-Alkylation of Aldehydes by Photoredox Organocatalysis: Rapid Access to Pharmacophore Fragments from β-Cyanoaldehydes**

*Eric R. Welin, Alexander A. Warkentin, Jay C. Conrad, and David W. C. MacMillan**

Abstract: *The combination of photoredox catalysis and enamine catalysis has enabled the development of an enantioselective α-cyanoalkylation of aldehydes. This synergistic catalysis protocol allows for the coupling of two highly versatile yet orthogonal functionalities, allowing rapid diversification of the oxonitrile products to a wide array of medicinally relevant derivatives and heterocycles. This methodology has also been applied to the total synthesis of the lignan natural product (−)-bursehernin.*

The enantioselective α-alkylation of carbonyl compounds with sp^3-hybridized halide-bearing electrophiles has long been considered an elusive goal for practitioners of asymmetric catalysis.[1] Indeed, the most commonly employed strategy to achieve the stereoselective construction of α-alkyl carbonyls involves the coupling of auxiliary-based metal enolates with halo or tosyloxy alkanes.[2,3] A critical issue for the development of catalytic variants of this venerable reaction has been the insufficient electrophilicity of alkyl halides towards silyl or alkyl enol ether π-nucleophiles (enolate equivalents that are broadly employed in asymmetric catalysis). This limitation has mandated the use of lithium-, sodium-, or cesium-derived enolates for auxiliary controlled carbonyl α-functionalization at higher carbonyl oxidation states. Recently, however, the application of secondary amine organocatalysts has overcome several of these constraints by the direct use of aldehydes or ketones in a variety of chiral enamine α-functionalization reactions.[4] As one example, our laboratory disclosed the synergistic merger of enamine catalysis with visible-light photoredox catalysis, wherein a ruthenium photocatalyst is used to generate highly electrophilic alkyl radicals derived from simple α-bromoesters and ketones.[5] Since that time, the field of photoredox catalysis as applied to organic synthesis has received considerable attention[6] and we have disclosed its successful application to the enantioselective α-trifluoromethylation,[7] α-benzylation,[8] and α-amination[9] of aldehydes.

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Recently, we questioned whether this dual photoredox-organocatalysis platform could be translated to the asymmetric catalytic alkylation of aldehydes using α-bromo cyanoalkyls, a protocol that would generate β-cyanoaldehydes in one step. As a critical design element, we recognized that α-bromo cyanoalkylating reagents would not be suitable electrophiles for most catalytic enolate addition pathways; however, the corresponding open-shell radicals, derived by one-electron reduction of α-bromonitriles, should readily undergo coupling with transiently generated chiral enamines. In addition, the nitrile functional group offers rapid access to a large array of carbonyl, amine, or imidate motifs,[10] and as such, β-cyanoaldehydes can be readily translated to lactones, pyrrolidines, lactams, and cyanoalcohols—pharmacophore fragments that are ubiquitous in medicinal chemistry.[11] Herein we report the first enantioselective α-cyanoalkylation of aldehydes via the synergistic combination of photoredox and organocatalysis (Figure 1).[12] Furthermore, we demonstrate the application of this new dual catalysis platform to the rapid and stereoselective construction of cyclic and acyclic motifs of broad value to the chemistry of drug discovery.

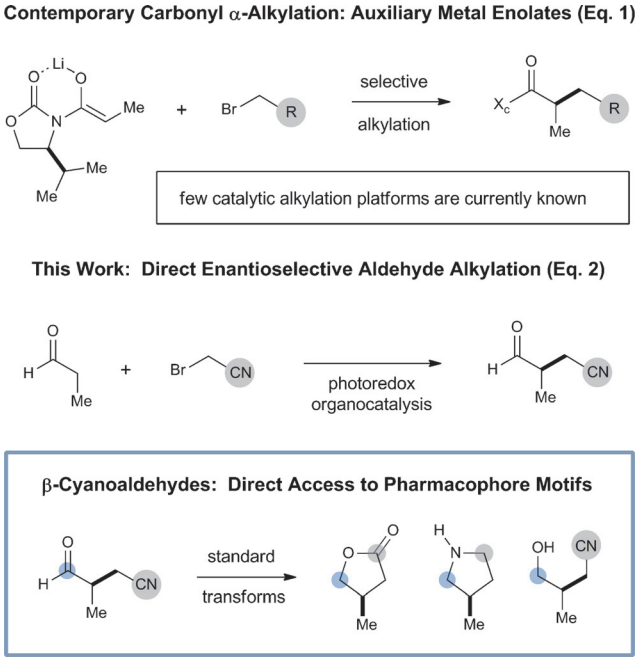
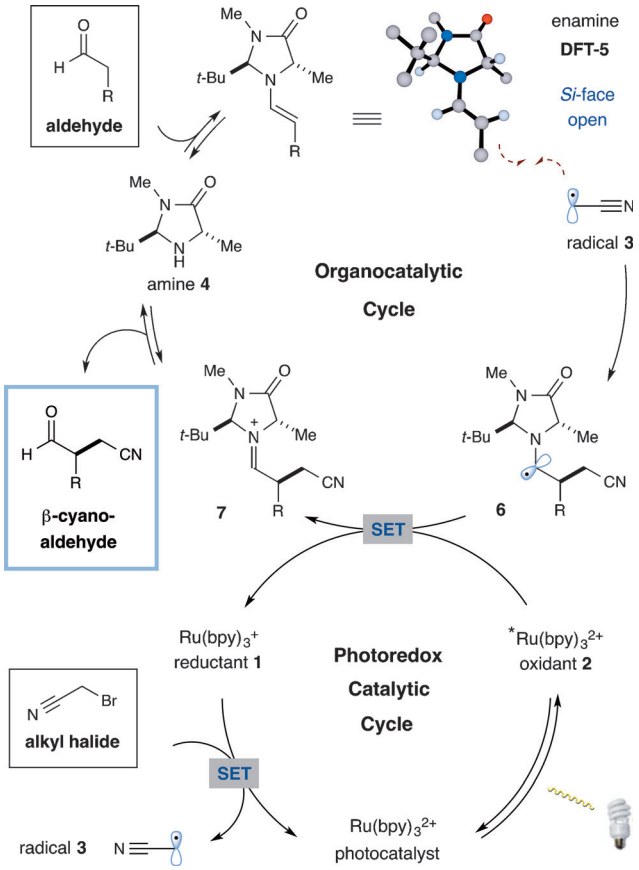


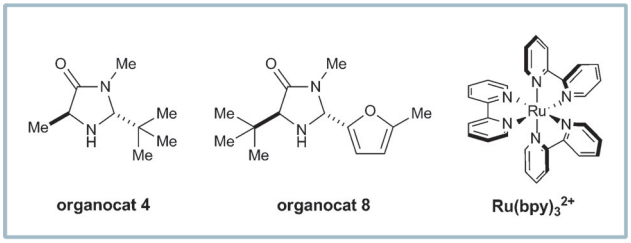
Figure 1. Photoredox organocatalysis α-cyanoalkylation of aldehydes.

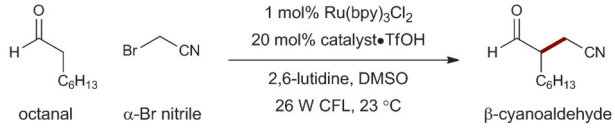
We envisioned that our cyanoalkylation dual catalysis mechanism would proceed as depicted in Scheme 1. Single-



Scheme 1. Catalytic cycle for aldehyde α-cyanoalkylation.

Table 1: Optimization of the photoredox organocatalytic addition.





Entry	Solvent	Concentration [M]	Catalyst	Yield [%]	*ee* [%][a]
1	DMF	0.5	**4**	72	93
2	CH_3CN	0.5	**4**	62	92
3	CH_3NO_2	0.5	**4**	28	94
4	DMSO	0.5	**4**	84	95
5	DMSO	0.5	**8**	85	95
6	DMSO	4	**8**	90	95
7	DMSO	4	**4**	95[b]	95
8	DMSO	4	**4**	90[c]	95
9	DMSO	4	**4**	74[d]	95

[a] Yield and enantiomeric excess determined by chiral GLC analysis of the aldehyde product using *p*-methoxyphenylacetone as internal standard. Reactions were performed with five equivalents of octanal unless otherwise noted. [b] Yield of isolated product. [c] Three equivalents of octanal. [d] One equivalent of octanal.

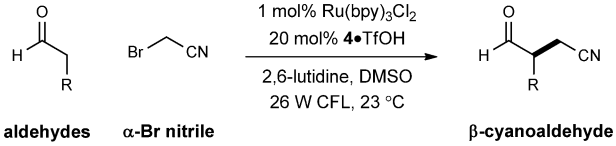
electron reduction of the bromonitrile species by the strongly reducing $Ru(bpy)_3^+$ ion **1**[13] ($E_{1/2}^{II/I} = -1.33$ V vs. SCE in CH_3CN for $Ru(bpy)^+$;[14] $E_{1/2}^{red} = -0.69$ V vs. SCE in DMF for bromoacetonitrile[15]) should provide the cyanoalkyl radical **3** and bromide ion after fragmentation. Simultaneously, the organocatalytic cycle would initiate by condensation of amine catalyst **4** with an aldehyde to generate a chiral enamine. Computational studies reveal that the lowest-energy conformation of the enamine **DFT-5** is found to position the π-nucleophilic C=C system distal to the large *tert*-butyl group on the imidazolidinone catalyst framework. Effective shielding of the *Re* face of the enamine by the pendent methyl group of the organocatalyst requires coupling to the electron-deficient radical **3** via the enamine *Si* face, thereby generating α-amino radical **6**, which is poised to re-engage the photoredox catalytic cycle. Photoexcitation of $Ru(bpy)_3^{2+}$ generates the oxidizing species **2** ($E_{1/2}^{*II/I} = +0.77$ V vs. SCE in CH_3CN),[14] which is well suited to perform a single-electron oxidation of α-amino radical **6** ($E_{1/2}^{red} = -0.92$ to -1.12 V vs. SCE)[16] thereby delivering iminium ion **7**; hydrolysis thereafter provides the α-cyanoalkylated aldehyde product while regenerating amine **4**, thus completing the organocatalytic cycle.

We chose to initiate our α-cyanoalkylation studies by exposing octanal, α-bromoacetonitrile, $Ru(bpy)_3Cl_2$, and imidazolidinone catalyst **4** to a 26 W CFL light source.[6] To our great delight, the desired asymmetric bond formation was realized in 72% yield and with excellent enantioselectivity (Table 1, entry 1, 93% *ee*). Evaluation of a variety of high-dielectric solvents identified dimethyl sulfoxide (DMSO) as the optimal medium, while increasing the reaction concentration provided excellent levels of both yield and enantioselectivity (entry 7, 95% yield, 95% *ee*). Notably, high-throughput analysis of a 96-member organocatalyst library identified the novel *tert*-butyl-furyl substituted imidazolidinone **8** as a viable alternative to catalyst **4** (entry 6, 90% yield, 95% *ee*). Finally, reducing the aldehyde stoichiometry to 1–3 equivalents could be tolerated without significant impact on yield or enantiocontrol (entries 8–9, 74–90% yield, 95% *ee*).

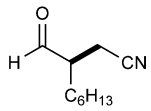
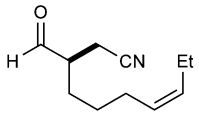
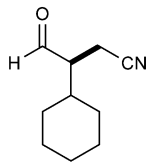
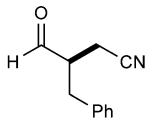
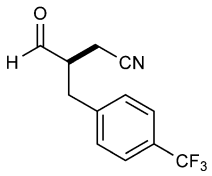
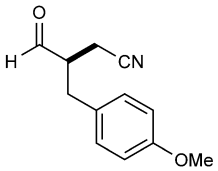
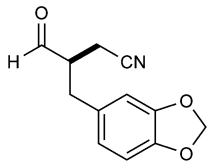
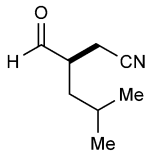
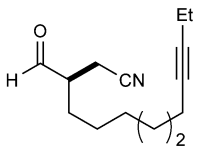
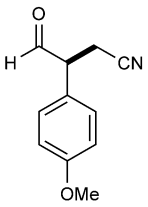
Using the optimal conditions identified in Table 1, we have demonstrated that our alkylcyanation reaction is quite general in scope with respect to the aldehyde component (Table 2). For example, aldehydes bearing aryl rings and significant steric bulk were well tolerated (**11**–**16**, **18**, 79–97% yield, 92–96% *ee*). Interestingly, intramolecular radical cyclization was not observed when aldehydes bearing pendent π-bonds were used (**10** and **17**, 68–90% yield, 91–95% *ee*). Finally, *p*-methoxyphenylacetaldehyde represents an intriguing addition to the scope of aldehydes in the transformation, as the alkylcyano product contains a tertiary α-formyl benzylic stereocenter, a motif typically prone to facile racemization (**18**, 80% yield, 90% *ee*).

We next investigated the scope of the α-bromonitrile alkylating component in this new dual catalysis bond-forming reaction. While bromoacetonitrile is an ideal coupling partner, we were also delighted to find that bromocyano

Table 2: Enantioselective α-cyanoakylation: aldehyde scope.

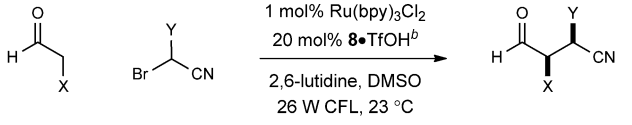


aldehydes **α-Br nitrile** **β-cyanoaldehyde**

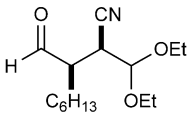
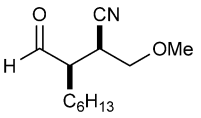
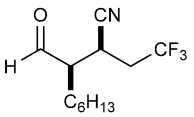
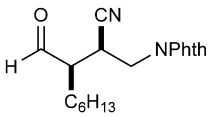
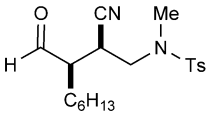
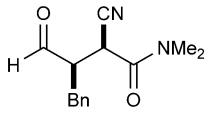
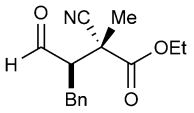
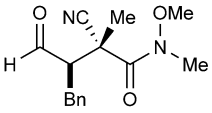
Product yield [%], (*ee* [%])[a]	Product yield [%], (*ee* [%])[a]
 **9** 95, (95)	 **10** 90, (95)
 **11** 79, (92)	 **12** 92, (93)
 **13** 95, (94)	 **14** 97, (96)
 **15** 94, (94)	 **16** 81, (95)
 **17** 68, (91)	 **18**[b] 80, (90)

[a] Yield of isolated aldehyde product. Enantiomeric excess determined by chiral GLC, HPLC, or SFC analysis on the aldehyde or the corresponding alcohol (see the Supporting Information). [b] Reaction performed at −20 °C. Product isolated as the corresponding alcohol after $NaBH_4$ reduction of the crude reaction mixture.

Table 3: Evaluation of the cyanobromide coupling partner.



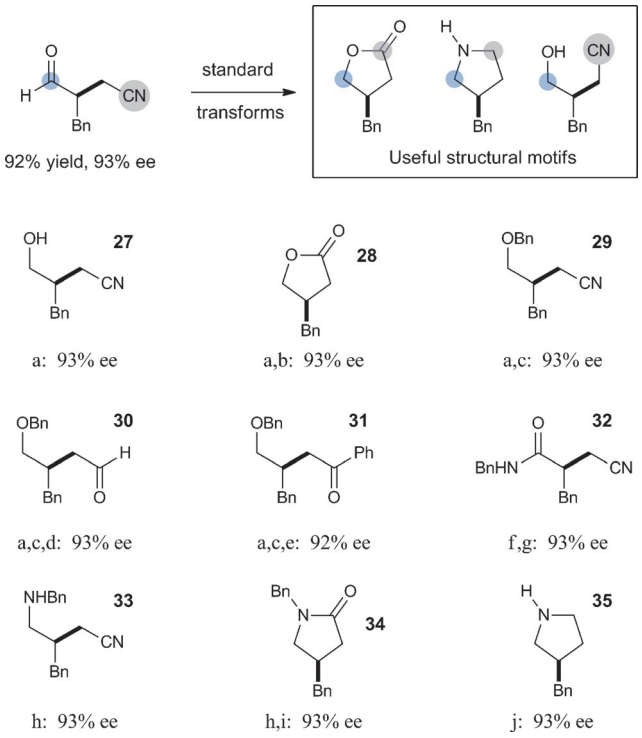
aldehydes **α-Br nitriles** **β-cyanoaldehyde**

Product yield [%], (*ee* [%])[a]	Product yield [%], (*ee* [%])[a]
 **19** 88, (98)	 **20** 79, (94)
 **21** 85, (95)	 **22** 86, (98)
 **23** 73, (95)	 **24** 78, (93)
 **25** 88, (93)	 **26** 77, (98)

[a] Yield of isolated product. Diastereomeric ratios (dr) 1–3:1, determined by ^1H NMR analysis, see the Supporting Information. Products were isolated as the aldehyde and further derivatized to determine enantiomeric excess (see the Supporting Information). [b] Catalyst added as the solid free amine; 20 mol% 2,6-lutidinium triflate was added as a source of the acid co-catalyst.

systems bearing diverse substitution patterns couple in high efficiency and excellent enantioselectivity (Table 3, 73–88% yield, 93–98% *ee*). It should be noted that imidazolidinone **8** was the preferred amine catalyst when substituted cyanoalkyls were employed.[17] Notably, fully substituted bromonitriles coupled efficiently, generating all-carbon quaternary stereocenters with excellent enantiocontrol albeit with modest diastereoselectivity (**25** and **26**, >93% *ee*).

Having examined the scope of both reaction partners, we next explored the breadth of pharmacophore fragments that could be accessed readily using these enantioenriched cyanoaldehyde building blocks. As illustrated in Scheme 2, alcohols, ethers, lactones, aldehydes, ketones, amides, amines, and lactams could be constructed in a straightforward manner in under three steps.[18] Intriguingly, we found that the nitrile could be hydrogenated under Raney Nickel conditions and achieve in situ cyclization of the amine on the pendent aldehyde moiety; further reduction of the resulting iminium ion generates (*R*)-3-benzylpyrrolidine (**35**) in a single step in



Scheme 2. Elaboration of cyanoalkylation products to useful motifs. Conditions: a) $NaBH_4$, MeOH, CH_2Cl_2, 84%, 93% *ee*. b) MeOH, conc. HCl, 100°C, 88%, 93% *ee*. c) NaH, BnBr, DMF, 85%, 93% *ee*. d) DIBAL-H, Et_2O, 83%, 93% *ee*. e) Mg, I_2, PhBr, Et_2O, then THF, 1 M HCl, 88%, 92% *ee*. f) $NaClO_2$, NaH_2PO_4, THF, *t*BuOH, 2-methyl-2-butene, H_2O, product not isolated. g) $BnNH_2$, HOBt·H_2O, NMM, EDCI·HCl, THF, 48%, 93% *ee* for two steps. h) $BnNH_2$, $NaBH(OAc)_3$, DCE, 77%, 93% *ee*. i) 1 mol% Parkins' catalyst, diglyme, 160°C, 93%, 93% *ee*. j) *p*-TsOH·H_2O, Raney Nickel 2400, H_2, EtOH, 81%, 93% *ee*. Bn = benzyl, DMF = dimethylformamide, DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran, HOBt = 1-hydroxybenzotriazole, EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, OAc = acetate, and DCE = 1,2-dichloroethane.

81% yield.[19] Most important, no erosion of enantiopurity (<1%) was observed in any of these synthetic elaboration studies.

Finally, to demonstrate the utility of our novel alkylcyanation technology, we undertook a short synthesis of (−)-bursehernin (**37**), a lignan natural product of proven biological activity (Scheme 3).[20] Employing our standard photoredox-amine catalysis protocol, exposure to sodium borohydride and cyclization under basic conditions provided the lactone **36**. The four-step synthesis of (−)-bursehernin was then completed via a highly selective α-alkylation using 3,4-dimethoxybenzyl bromide, generating the natural product in 80% yield overall from bromoacetonitrile.

Keywords: aldehydes · alkylation · organocatalysis · photoredox catalysis · total synthesis

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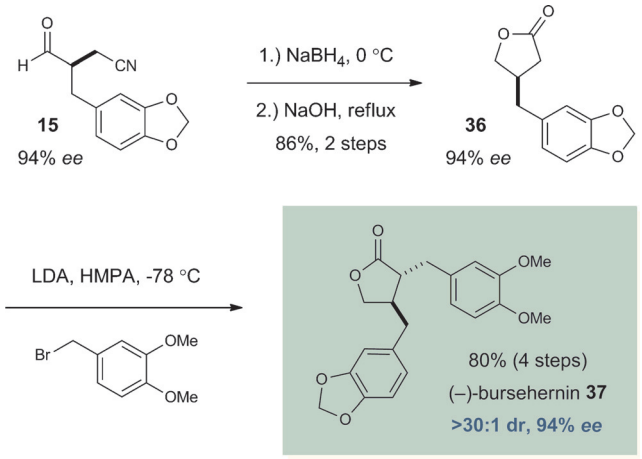

Scheme 3. Total synthesis of (−)-bursehernin. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide.

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