Enantioselective α-Benzylation of Aldehydes via Photoredox Organocatalysis

Hui-Wen Shih, Mark N. Vander Wal, Rebecca L. Grange, and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544

Received July 25, 2010; E-mail: dmacmill@princeton.edu

Abstract: The first enantioselective aldehyde α-benzylation using electron-deficient aryl and heteroaryl substrates has been accomplished. The productive merger of a chiral imidazolidinone organocatalyst and a commercially available iridium photoredox catalyst in the presence of household fluorescent light directly affords the desired homobenzylic stereogenicity in good to excellent yield and enantioselectivity. The utility of this methodology has been demonstrated via rapid access to an enantioenriched drug target for angiogenesis suppression.

The benzylic alkylation of chiral enolates has become a mainstay transformation in chemical synthesis, mainly due to the seminal research efforts of Evans, Oppolzer, Seebach, and Myers.[1] Surprisingly, however, catalytic enantioselective variants of this venerable reaction remain confined to a small but valuable group of substrate types. Phase transfer benzylation of glycine-derived imines,[2] chiral triamine ligation of ketone-derived lithium enolates,[3] and the use of Jacobsen's Cr(salen) complex with preformed stannous enolates[4] are among the most successful examples.[5] Direct organocatalytic methods to form α-benzylated aldehydes have also been reported wherein the electrophilic partner requires multiple and/or electron-rich aryl rings (to enable the intermediate formation of stabilized benzylic carbocations).[6] Recently, our laboratory introduced a new mode of activation termed photoredox organocatalysis,[7,8] the mechanistic foundation of which relies on the propensity of electrophilic radicals (derived from photocatalytic reduction of alkyl halides) to combine with facially biased enamines (derived from aldehydes and a chiral amine catalyst). Inspired by this strategy, we hypothesized that the enantioselective α-benzylation of aldehydes might also be possible via the marriage of these activation pathways. Herein, we present a new direct and enantioselective catalytic protocol for the α-alkylation of aldehydes, a transformation that is successful with a wide array of simple monoaryl[9] and monoheteroaryl methylene halides.
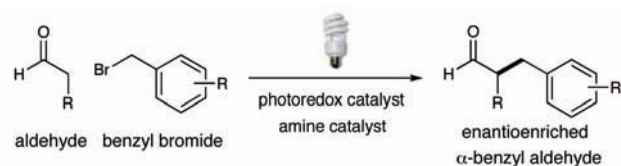
Design Plan. As detailed in Figure 1, it has been established that commercially available *fac*-Ir(ppy)₃ (**1**) (ppy = 2-phenylpyri-
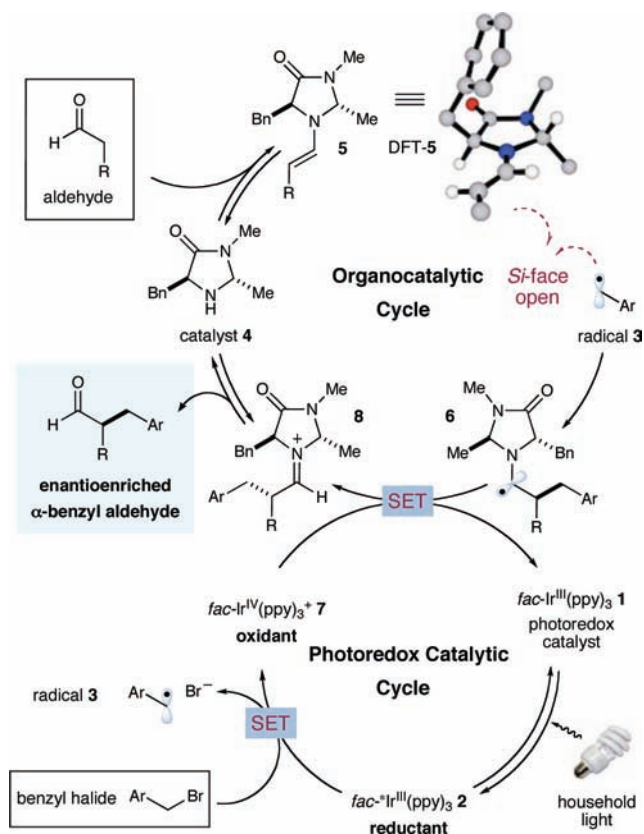

Figure 1. Proposed catalytic cycle for aldehyde α-benzylation.

dine), commonly used as a green triplet emitter in OLEDs, can readily accept a photon from weak fluorescent light to generate the strong reductant excited state *fac*-*Ir(ppy)₃ (**2**) ($E_{1/2} = -1.73$ V vs saturated calomel electrode (SCE) in CH₃CN).[10] We hoped that single electron transfer (SET) from *fac*-*Ir(ppy)₃ to a suitable benzylic bromide might render an aromatic radical anion that would rapidly undergo σ-bond cleavage to afford the bromide anion and an electrophilic benzyl radical **3**. Within the same time frame, condensation of an aldehyde substrate with imidazolidinone catalyst **4** should form a highly π-nucleophilic enamine **5** which should then combine with the electron-deficient radical **3** to enantioselectively forge the crucial homobenzylic center. Rapid oxidation of the resultant α-amino radical[11] **6** by *fac*-Ir(ppy)₃⁺ (**7**) ($E_{1/2} = 0.77$ V vs SCE in CH₃CN)[10] would then close the redox cycle while regenerating the photocatalyst *fac*-Ir(ppy)₃ (**1**). Moreover, subsequent hydrolysis of iminium **8** would reconstitute the organocatalyst **4** while liberating the enantioenriched α-benzyl aldehyde adduct.

Evaluation of this tandem catalysis strategy was first examined with octanal, imidazolidinone catalyst **9**, *fac*-Ir(ppy)₃ (**1**), a 26 W compact fluorescent lamp, and 2,4-dinitrobenzyl bromide, benzyl bromide, or 4-(bromomethyl)pyridine as the alkylating reagent. As

Table 1. Evaluation of Amine Catalyst for Benzylation
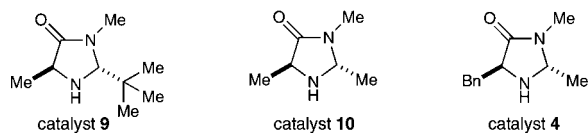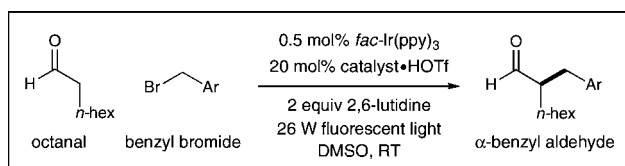
entry	Ar	catalyst	% yield[a]	% ee[b]
1	Phenyl	9	0	ND
2	2,4-(NO₂)₂C₆H₃	9	74	97
3	2,4-(NO₂)₂C₆H₃	10	93	82
4	2,4-(NO₂)₂C₆H₃	4	94	92
5[c]	4-Pyridinyl	9	0	ND
6[c]	4-Pyridinyl	10	81	78
7[c]	4-Pyridinyl	4	86	90

[a] Isolated yields. [b] Enantiomeric excess determined by chiral HPLC. [c] 4-(Bromomethyl)pyridine added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine.

shown in Table 1, initial experiments revealed that the proposed benzylation was indeed possible; however, the coupling component was restricted to the most electron-deficient dinitro-aryl system (entry 2). Intriguingly, the use of benzyl bromide resulted in the complete recovery of starting materials[12] while 4-(bromomethyl)-

Table 2. Asymmetric Aldehyde α-Benzylation: Aldehyde Scope

[a] Stereochemistry assigned by chemical correlation or by analogy. [b] Enantiomeric excess determined by chiral SFC or HPLC. [c] Substrate added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine. The free base organocatalyst was used. [d] Isolated yield of the corresponding alcohol.

Table 3. Asymmetric Aldehyde α-Benzylation: Bromide Scope


[a] Stereochemistry assigned by chemical correlation or by analogy. [b] Enantiomeric excess determined by chiral SFC or HPLC. [c] 30 mol% organocatalyst used. [d] Performed at 15 °C using Ru(bpy)₃Cl₂ as the photoredox catalyst; ref 14. [e] Substrate added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine. The free base organocatalyst was used. [f] Yield determined by ¹H NMR. [g] Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ was employed as the photoredox catalyst; ref 15. [h] Isolated yield of the corresponding alcohol.

pyridine rapidly decomposed under photoredox conditions (entries 1, 5). These data suggest that electron-neutral benzylic halides do not readily undergo the initial reduction step, while the pyridinium radical is formed but does not couple with the enamine derived from amine **9**. To address this latter limitation, we next examined amine catalysts of diminished steric demand with the presumption that a higher concentration and increased spatial exposure of the enamine intermediate should increase the rate of the critical radical-olefin addition step. Indeed, the pseudo-C_2-symmetric catalyst **10** (wherein the *tert*-butyl substituent has been replaced by a methyl group) does enable the pyridinium methylene bromide to become a viable coupling partner, albeit with low selectivities (entry 6, 81% yield, 78% ee). Enantiocontrol is regained, however, when the benzyl, methyl disubstituted amine **4** is employed (entry 7, 90% ee), a catalyst that likely operates via the preferred *E*-enamine geometry with shielding of the π-nucleophilic *Re*-face by the benzylic moiety on the catalyst framework (DFT-**5**).[13] The superior levels of scope, induction, and efficiency exhibited by the combination of catalysts **4** and *fac*-Ir(ppy)₃ (**1**) in DMSO at 23 °C prompted us to select these conditions for further exploration.

We next performed a series of experiments to determine the scope of the aldehydic component in this asymmetric benzylation protocol.

As revealed in Table 2, these mild redox conditions are compatible with a wide range of functional groups, including ethers, amines, imides, carbamates, and aromatic rings (72−91% yield, 87−90% ee). Moreover, significant variation in the steric demand of the aldehyde substituent can be accommodated without loss in enantiocontrol (entries 4 and 5, ≥73% yield, 90% ee).

Enantioselective synthesis of a bioactive drug candidate
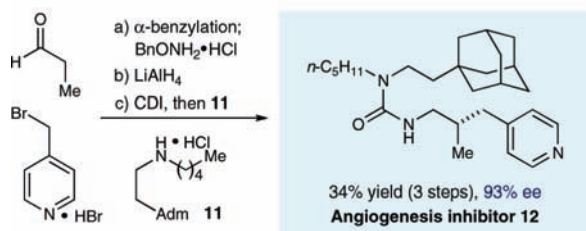
We have found that a broad range of electron-deficient aryl and heteroaryl methylene bromides also participate in this enantioselective benzylation reaction (Table 3). For example, benzyl systems that incorporate a nitro-substituent with other electron-withdrawing groups such as nitriles and esters (Table 3, entries 1−3) are well-tolerated. Moreover the 1,2-nitro-fluoro aryl ring can serve to produce a suitably electrophilic radical without the intervention of S_NAr byproducts (entry 3). Perhaps more notable with respect to medicinal agent synthesis, a large range of heteroaryl rings can be successfully employed such as pyridines, quinolines, benzimidazoles, pyrimidines, and triazines. As highlighted in entries 4 and 5, bromomethyl pyridines that have electron-donating substitution (entry 5, 2-methyl, 91% ee) or electron-withdrawing groups (entry 4, 5-nitro, 90% ee) are both competent in this enantioselective coupling. Moreover, fused bicycles such as 4-quinolinyl and 2-benzimidazolyl also perform well (81−90% yield, 82−88% ee, entries 6, 10). We postulate that, for substrates with a basic nitrogen (4-pyridinyl, and entries 5−6, 10),[16] substrate protonation facilitates the initial reduction step[17] and thereafter enhances the electrophilicity of the resulting radical intermediate. However, heterocycles containing two nitrogens, such as 2-pyrazinyl and 4-pyrimidinyl, and three nitrogens, such as 2-triazinyl—which all lack a basic nitrogen—also react with good efficiency and excellent enantioselectivity (68−78%, 87−91% ee, entries 7−9).[18]

We fully expect that the α-heteroarylmethyl aldehyde products generated in this study will be of value for the generation and testing of medicinal agents. To highlight this possibility, we have applied our new catalytic enantioselective benzylation strategy to the synthesis of the angiogenesis inhibitor 12,[19] a drug candidate that was developed for the treatment of diseases such as diabetic retinopathy and tumor proliferation. As illustrated above, exposure of propionaldehyde and 4-(bromomethyl)pyridine to our photoredox coupling protocol followed by in situ oxime formation yields the α-methylene pyridyl intermediate in 82% yield and 93% ee. Subsequent oxime reduction followed by urea coupling with amine 11 (available in two chemical steps) allows the rapid construction of angiogenesis inhibitor 12 in only three linear steps (34% overall yield, 93% ee).

In an effort to provide insight into the mechanistic details of this tandem catalysis coupling, we have performed several fluorescence quenching experiments (Stern−Volmer studies) with our fac-Ir(ppy)₃ photoredox catalyst (Figure 2). Notably, fac-*Ir(ppy)₃ oxidation of enamine 5 is not observed and, as such, cannot be the first step in the photocatalytic cycle (in contrast to previous studies from our laboratory that centered upon Ru(bpy)₃Cl₂).[7] Instead, both
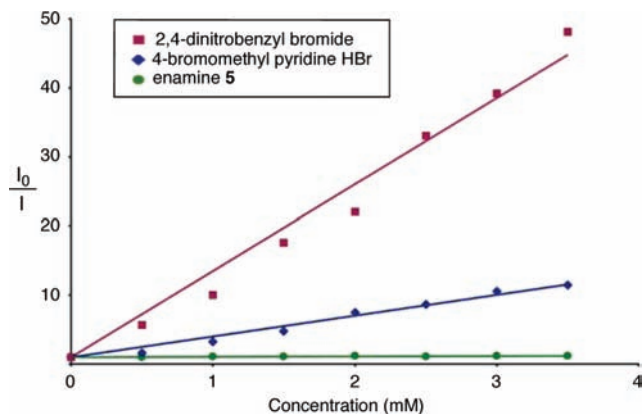

Figure 2. Fluorescence quenching by reaction substrates.

aryl and heteroaryl methylene bromides display efficient quenching of the fac-*Ir(ppy)₃ excited state, strongly suggesting that the electron transfer event occurs directly between fac-*Ir(ppy)₃ and the aryl coupling partner. This is in accord with the catalytic cycle set out in Figure 1.

In conclusion, the first enantioselective aldehyde α-benzylation using electron-deficient aryl and heteroaryl substrates has been accomplished. The productive merger of a novel imidazolidinone organocatalyst and a commercially available iridium photoredox catalyst directly allows the stereocontrolled formation of homobenzylic stereogenicity in good to excellent yield. This new alkylation reaction, which exhibits broad scope and wide functional group tolerance, has been successfully utilized for the rapid and enantioselective construction of a previously developed angiogenesis inhibitor in only three linear chemical steps.

Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361. (c) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197. (d) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603.
(2) (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (b) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222.
(3) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829.
(4) (a) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62. (b) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701.
(5) An intramolecular enamine alkylation strategy has been demonstrated; see: Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.
(6) (a) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8707. (b) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313. (c) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286.
(7) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.
(8) For recent examples of photoredox catalysis, see: (a) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (b) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (c) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756. (d) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (e) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (f) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (g) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368. (h) Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, *46*, 4985. (i) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**,

12, 3104. (j) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572.

(9) The racemic homolytic alkylation of stoichiometric enamines using *p*-nitrobenzyl chloride as radical precursor is known; see: Russell, G. A.; Wang, K. *J. Org. Chem.* **1991**, *56*, 3475.

(10) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.

(11) α-Amino radicals possess oxidation potentials in the range of −0.92 to −1.12 V vs SCE in CH_3CN; see: Wayner, D. D. M.; Dannenberg, J. J.; Griller, D. *Chem. Phys. Lett.* **1986**, *131*, 189.

(12) We recognized from the outset that this strategy might not be successful with electron-neutral aryl systems due to the high reduction potential of systems such as benzyl bromide ($E_{1/2}$ = −1.85 V vs SCE in CH_3CN) and the nucleophilic nature of the unsubstituted benzylic radical. For benzyl bromide reduction potential, see: Koch, D. A.; Henne, B. J.; Bartak, D. E. *J. Electrochem. Soc.* **1987**, *134*, 3062. For benzylic radical nucleophilicity, see: De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. *Org. Lett.* **2007**, *9*, 2721.

(13) DFT calculations were performed with the use of B3LYP/6-311+G(2d,2p)//B3LYP/6-31G(d).

(14) Reaction does proceed with Ir(III) catalyst, but with decreased yield. Ru(bpy)$_3$Cl$_2$ is a competent photoredox catalyst for these transformations but usually results in lower conversion; for photophysical properties, see: Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159.

(15) dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; see: Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A., Jr.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712.

(16) These compounds have pK_a values within 2 orders of magnitude of 2,6-lutidine, and the reduction potentials of the unprotonated species are too high to be reduced by the photocatalyst. For pK_a values in DMSO, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. For reduction potentials, see: Wiberg, K. B.; Lewis, T. P. *J. Am. Chem. Soc.* **1970**, *92*, 7154.

(17) Thévenot, D.; Buvet, R. *J. Electroanal. Chem.* **1972**, *39*, 429.

(18) The parent bromomethyl-heterocycles lacking additional substitution (e.g., 2-(bromomethyl)pyrazine) are reported to be unstable; for pyrimidines, see: (a) Brown, D. J.; Waring, P. *Aust. J. Chem.* **1974**, *27*, 2251. For pyrazines, see: (b) Sasaki, K.; Sugou, K.; Miyamoto, K.; Hirai, J.; Tsubouchi, S.; Miyasaka, H.; Itaya, A.; Kuroda, Y. *Org. Biomol. Chem.* **2004**, *2*, 2852. For triazines, see: (c) Von Angerer, S. *Sci. Synth.* **2003**, *17*, 449.

(19) Matsuoka, H.; Nishimura, K.; Seike, H.; Aono, H.; Murai, M. Preparation of pyridylalkylurea derivatives as angiogenesis inhibitors. U.S. Patent 2008/0161270 A1, July 3, 2008.

JA106593M