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Radical α -C–H Cyclobutylation of Aniline Derivatives

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Abstract

A catalytic system has been developed for the direct alkylation of α -C–H bonds of aniline derivatives with strained C–C σ -bonds. This method operates through a photoredox mechanism in which oxidative formation of aminoalkyl radical intermediates enables addition to a bicyclobutane derivative, giving rise to α -cyclobutyl *N*-alkylaniline products. This mild system proceeds through a redox- and proton-neutral mechanism and is operational for a range of substituted arylamine derivatives.

Graphical Abstract

Keywords

photoredox reaction; catalysis; C–C bond activation; anilines; alkylation; iridium catalysis

The high stability of C–C single bonds typically renders them chemically inert; however, conformationally strained-ring systems display unique reactivity profiles. Early work by Wiberg and co-workers and by Gaoni demonstrated that a range of strained polycyclic hydrocarbons (some of which are shown in Figure 1) can be accessed synthetically,^{1–3} and that they can serve as effective alkylating agents.^{4,5} Indeed, because installation of cyclobutyl groups (cyclobutylation) can be accomplished through direct addition to bicyclo[1.1.0]butane (BCB) derivatives, this represents a potentially valuable method for the synthesis of cyclobutane-containing natural products or drug candidates.

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This paper is dedicated to Jürgen Klopp (manager of Liverpool F.C.) for his inspirational leadership.

Supporting Information

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In addition to anionic nucleophiles,^{6–8} organometallics,^{9–11} and amines,^{12,13} strained BCBs are effective coupling partners for radical species.^{7,14} Over the past few years, our laboratory has been interested in developing new methods that permit selective reactions through the use of photoredox catalysis. As part of this program, we recently developed a system for the direct addition of nonactivated amines to peptides through the formation of the corresponding α -amino radicals.¹⁵ This process is highly selective and it functions through a redox- and proton-neutral mechanism, such that stoichiometric additives are not required. We questioned whether these aminoalkyl radical intermediates¹⁶ could be intercepted by strain-activated BCB derivatives in a direct cyclobutylation reaction with amines. Although a number of impressive methods for cyclobutylation of radical intermediates have been described, most recently by the groups of Lin¹⁷ and Aggarwal,¹⁸ this approach (outlined in Figure 1) would be unique, in part, because it would potentially function on a range of nonactivated amine-containing substrates, without the need for programmed radical formation (i.e., halogen installation, etc.).

We considered the catalytic pathway shown in Figure 1, in which photoinduced electron transfer from the amine substrate to a photoredox catalyst would give rise to a radical cation. Deprotonation of the newly acidified C–H bond would afford a key α -amino radical species.^{20–23} Attack of this intermediate species on a strain-activated bicyclo[1.1.0]butane would afford a new C–C bond, and single-electron reduction and protonation would deliver the desired α -cyclobutylamine. This system would operate in a redox- and proton-neutral manner, without the need for exogenous chemical additives.

To evaluate the feasibility of this proposed transformation, we treated *N,N*-dimethylaniline with a small series of BCB reagents **1a–c** to afford the corresponding cyclobutylated products **2a–c** (Table 1). In the presence of 1 mol% of Ir[dF(CF₃)ppy]₂(dtbbpy)·PF₆ [**P1**; dF = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine] and blue light in *N,N*-dimethylacetamide (DMA), phenylsulfone **1a** gave the desired product **2a** in a promising yield (28%, as determined by NMR with an internal standard). Increasing the electron-withdrawing capacity of the sulfonyl activating group resulted in improved reactivity with aminoalkyl radicals. Specifically, the fluorinated phenylsulfone derivatives **1b** and **1c** gave the corresponding cyclobutane products **2b** and **2c** in yields of 64 and 69%, respectively. In this system, the aniline substrate was used as the excess reagent (five equivalents with respect to the BCB reagent) to suppress further activation and cyclobutylation of the desired products **2**. Importantly, this process was not operational in the absence of a photoredox catalyst or light (Table 1, entries 1 and 2; 0% yield). Other catalysts could also be employed to accomplish this transformation, although less-oxidizing iridium catalysts (such as **P2**; entry 3: 35% yield) or organic dyes [including penta-9*H*-carbazol-9-ylbenzonitrile (5CzBn; **P3**) (entry 4: 64% yield)] were less efficient across an array of substrates. A variety of aprotic organic solvents could be utilized here with acceptable levels of reaction efficiency (entries 5–7; 46–51% yield).

Having identified an effective protocol for the α -alkylation of anilines with BCB **1c**, we evaluated the substrate scope of this process (again utilizing **1c** as the limiting reagent with five equivalents of the aniline substrate).²⁴ As shown in Table 2, electron-deficient dimethylaniline derivatives reacted under standard conditions to give the corresponding

products **3** and **4** in yields of 65 and 46%, respectively. Cyclic aniline derivatives were also effectively transformed into the corresponding cyclobutylated products. For example, *N*-phenylpyrrolidine reacted well to afford **5** in 83% isolated yield. These conditions were less effective for the coupling of *N*-phenylpiperidine (which gave **6** in 33% yield, with 55% remaining starting material), presumably due to increased steric constraints. However, seven- and eight-membered saturated nitrogen heterocycles were excellent substrates, giving rise to the corresponding cyclobutanes **7** and **8** in near-quantitative yield (96% in each case).²⁵ In accord with earlier reports,²¹ aniline derivatives with electron-donating groups in the *ortho*- or *para*-positions were not reactive in this system, where coupling attempts uniformly returned the starting materials. However, these conditions were effective for the transformation of electron-deficient aniline derivatives. Alkylation of a variety of *N*-arylpiperidines occurred smoothly; a methoxy substituent was well tolerated in the *meta*-position (**9**; 61% yield), as were fluoro and bromo substituents (**10–12**; 57–79% yield). As expected, the methoxycarbonyl- and nitrile-substituted phenylpiperidines were excellent substrates for this transformation, giving rise to products **13** and **14** in yields of 77 and 90%, respectively.

In most cases, the products were isolated as roughly equal (<2:1) mixtures of *cis*- and *trans*-cyclobutane stereoisomers. Slightly higher selectivity was observed in a few cases (**7**, **8**, and **11**: ~2.3:1 ratio); although chromatographic separation of these diastereomers was often difficult, we were able to purify the major isomer of **7**. Crystallization of this isomer permitted its analysis by X-ray crystallography, which demonstrated that the major isomer in this case was the *cis*-cyclobutane, consistent with protonation occurring from the less sterically hindered face of the cyclobutane ring. The synthetic utility of arylsulfonylcyclobutanes has been extensively demonstrated by the Baran group.¹³ In line with these reports, reductive desulfonylation of product **5** occurred smoothly in the presence of excess magnesium in methanol at room temperature to give 71% yield of the cyclobutyl product **15**, as shown in Scheme 1.

In summary, we have developed a mild system for the direct C–H cyclobutylation of aniline derivatives. This process operates through formation of an α -amino radical, followed by direct addition to a strained BCB derivative. The dis-closed protocol readily functionalizes a range of *N*-aryl amines and heterocyclic compounds of various ring sizes. In accord with previous reports, electron-deficient aniline derivatives were shown to be efficient coupling partners. Because the resulting sulfonyl cyclobutane products have been shown to be capable of being manipulated in a number of ways, we anticipate this process will be an attractive method for the generation of a range of α -cyclobutyl amine derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (24). α -Cyclobutylanilines 2–14; General ProcedureA screw-top test tube equipped with a stirrer bar was charged with $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbbpy})]\cdot\text{PF}_6$ (1 mol%), **1C** (1 equiv), and, if solid, the appropriate aniline (5 equiv). The tube was sealed with a PTFE/silicon septum and connected to a Schlenk line. The atmosphere was exchanged by applying a vacuum and backfilling with N_2 (this process was conducted a total of three times). Under a N_2 atmosphere, the tube was charged by syringe with previously degassed solvent (DMA; 2 mL/mmol **1C**) and, if liquid, the appropriate aniline. The resulting solution was stirred at 700 rpm and irradiated with blue LEDs

(4 cm from the lamp) for 16 h. The reaction was then quenched with sat. aq NaHCO₃ (10 mL), and the mixture was extracted with EtOAc (3 × 15 mL). The combined extracts were washed sequentially with 5% aq LiCl (3 × 15 mL) and brine (2 × 15 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by chromatography (silica gel) to give the desired product. See the Supporting Information for full details, along with physical and spectroscopic data for the products.³²⁶**1C**₂₂**1C**₃₂₄

- (25). 2-{3-[(3,5-Difluorophenyl)sulfonyl]cyclobutyl}-1-phenylazepane (*cis*-7) By following general procedure, the reaction of **1C** (116.6 mg, 0.5 mmol, 1 equiv), 1-phenylazepane (450 µl, 2.5 mmol, 5 equiv), and [Ir{dF(CF₃)ppy}₂(dtbbpy)]·PF₆ (6.4 mg, 0.005 mmol, 0.01 equiv), followed by purification by flash column chromatography [silica gel, EtOAc–hexanes (0–20%)], gave a clear oil; yield: 128.8 mg (64%). ¹H NMR (600 MHz, CDCl₃): δ = 7.38–7.32 (m, 2 H), 7.19 (dd, *J* = 8.5, 7.0 Hz, 2 H), 7.07–6.97 (m, 1 H), 6.72 (d, *J* = 8.3 Hz, 2 H), 6.61 (t, *J* = 7.2 Hz, 1 H), 3.86 (dt, *J* = 10.4, 6.9 Hz, 1 H), 3.63–3.52 (m, 2 H), 3.06 (dd, *J* = 15.6, 11.4 Hz, 1 H), 2.52–2.43 (m, 1 H), 2.41–2.30 (m, 2 H), 2.23 (dp, *J* = 11.9, 4.1 Hz, 1 H), 2.15 (dtd, *J* = 12.0, 7.9, 4.1 Hz, 1 H), 2.08 (dt, *J* = 14.4, 7.2 Hz, 1 H), 1.77–1.66 (m, 3 H), 1.60–1.52 (m, 1 H), 1.37–1.22 (m, 2 H), 1.22–1.13 (m, 1 H). ¹³C NMR (151 MHz, CDCl₃): δ = 162.8 (dd, *J* = 255.8, 11.4 Hz), 148.5, 141.3 (t, *J* = 7.8 Hz), 129.4, 115.1, 112.1–111.7 (m), 110.8, 109.4 (t, *J* = 24.9 Hz), 58.6, 53.2, 43.2, 34.3, 31.9, 29.8, 26.9, 26.3, 25.9, 24.8. ¹⁹F (376 MHz, CDCl₃): δ = –104.95 to –104.96 (m). ¹₃¹³₃¹⁹X-ray-quality crystals of *cis*-7 were obtained by Et₂O and hexane vapor diffusion. C₂₂H₂₅F₂NO₂S, *M_r* = 405.49, monoclinic, *P*₂₁/*n* (No. 14), *a* = 9.56610(10), *b* = 21.4256(3), *c* = 19.3969(2) Å, β = 96.1240(10)°, *V* = 3952.89(8) Å³, *T* = 102(4) K, *Z* = 8, *Z'* = 2, μ(MoK_α) = 0.200; 135731 reflections measured, 20640 unique (*R*_{int} = 0.0684), which were used in all calculations. The final *wR*₂ was 0.1495 (all data) and *R*_{*I*} was 0.0566 [*I* > 2σ(*I*)]. 2222522r1 ³_{aint21} Cambridge Crystallographic Data Centre (CCDC) contains the supplementary crystallographic data for compound *cis*-7. The data can be obtained free of charge from The CCDC via www.ccdc.cam.ac.uk/getstructures. 2-{3-[(3,5-Difluorophenyl)sulfonyl]cyclobutyl}-1-phenylazepane (*trans*-7) By following general procedure, the reaction of **1C** (116.6 mg, 0.5 mmol, 1 equiv), 1-phenylazepane (450 µl, 2.5 mmol, 5 equiv), and [Ir{dF(CF₃)ppy}₂(dtbbpy)]·PF₆ (6.4 mg, 0.005 mmol, 0.01 equiv), followed by purification by flash column chromatography [silica gel, EtOAc–hexanes (0–20%)], gave a clear oil; yield: 64 mg (32%). ¹H NMR (600 MHz, CDCl₃): δ = 7.40–7.35 (m, 2 H), 7.15 (dd, *J* = 8.9, 7.1 Hz, 2 H), 7.04 (tt, *J* = 8.4, 2.3 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 6.57 (t, *J* = 7.2 Hz, 1 H), 3.84 (td, *J* = 9.1, 6.4 Hz, 1 H), 3.69–3.58 (m, 2 H), 3.07 (ddd, *J* = 15.7, 11.5, 2.0 Hz, 1 H), 2.90–2.82 (m, 1 H), 2.66–2.58 (m, 1 H), 2.50–2.42 (m, 1 H), 2.24–2.13 (m, 2 H), 2.13–2.04 (m, 1 H), 1.74–1.65 (m, 3 H), 1.53–1.51 (m, 1 H), 1.37–1.22 (m, 2 H), 1.20–1.13 (m, 1 H). ¹³C NMR (151 MHz, CDCl₃): δ = 162.9 (dd, *J* = 255.9, 11.4 Hz), 148.8, 141.3 (t, *J* = 8.0 Hz), 129.4, 115.1, 111.9 (dd, *J* = 21.7, 6.5 Hz), 110.9, 109.4 (t, *J* = 24.9 Hz), 58.6, 54.7, 43.0, 36.2, 32.2, 29.6, 26.0, 25.7, 25.7, 24.7. ¹³₃¹⁹F NMR (376 MHz, CDCl₃): δ = –105.01 to –105.04 (m). ¹⁹₃

Highly Strained Carbocycles: Activated C–C Bonds

Bicyclic alkanes:

Strain energy:

68 kcal/mol

64 kcal/mol

55 kcal/mol

Goal: Amine cyclobutylation with strained carbocycles

Figure 1.

Strategy for cyclobutylation through addition to strained bicyclic alkanes. The strain energy for each molecule is derived by comparing δH_f with a hypothetical strainless model, as discussed by Wiberg.¹⁹

Scheme 1.
Reductive desulfonation of arylsulfonylcyclobutane **5**

Table 1Optimal Conditions for α -Cyclobutylation of *N,N*-Dimethylaniline

Entry	Deviation from above conditions (with 1c)	Yield (%) of 2c
1	Reaction without catalyst	0
2	Reaction without blue light	0
3	1 mol% Ir[(ppy) ₂ (dtbbpy)]-PF ₆ ^a (P2) as catalyst	35
4	5 mol% 5CzBn ^b (P3) as catalyst	64
5	MeCN as solvent	48
6	DCE as solvent	46
7	DMSO as solvent	51

^a ppy = 2-phenylpyridine.

Table 2

Scope of Anilines. ^a<2:1 dr, ^b2.3:1 dr.