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Endergonic addition of *N*-methylamines to aromatic ketones driven by photochemical offset of the entropic cost[†]

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Intermolecular addition reactions are generally accompanied by an entropic penalty due to the decrease of molecular numbers during the reaction, which sometimes makes the reaction endergonic. Here we demonstrate that such an endergonic reaction can be promoted with light-energy as a driving force; *N*-methylamines were added to aromatic ketones to produce aminoalcohols under UV-light irradiation. The reaction represents an obvious example showing that the photochemical approach is effective to offset such an entropic cost, and thereby to drive thermodynamically uphill addition reactions. Moreover the present reactions are highly expedient from the synthetic view point, being transition-metalcatalyst-free, scalable, highly atom economical, and regioselective. The product amines can be converted in one step to functional multi-arylated enamines, which are potentially valuable compounds in electronic materials.

Photoreactions and photocatalysis have received extensive attention in synthetic chemistry over the past few decades.¹ One prominent feature of photochemical approaches to synthetic chemistry is to make a thermodynamically uphill reaction feasible by using light energy as a driving force. Such a reaction is attractive not only as a method for the storage of solar energy in the form of chemical energy, but also as a synthetic method for the production of functional organic molecules. Several examples of light-driven uphill reactions, such as olefin isomerization, [2+2]cycloaddition and a few more, are known.² However, applications for light-driven reactions are still limited. Thus, to expand the field of such advantageous photoreactions, further efforts on reaction design based on thermodynamics are needed.

Intermolecular addition reactions to unsaturated bonds play a vital role in organic synthesis for the construction of functional molecules. Thermodynamically, these reactions are

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often entropically unfavorable because such bimolecular bond formation decreases the number of molecules in the reaction system.

If enthalpic gain cannot compensate for the entropy loss (negative $T\Delta S$), the reaction does not proceed spontaneously without input of external energy (endergonic reaction, $\Delta G > 0$, Scheme 1a).³ As a striking example of using a photochemical reaction to overcome such thermodynamic constraint, Murakami *et al.* reported the light-driven carboxylation of *o*-alkylphenyl ketones with carbon dioxide, which is the formal addition of a C–H bond to carbon dioxide (Scheme 1b).^{2g} Moreover, Knowles *et al.*



- Intermolecular bond formations often cause entropic penalty (ΔS < 0)

• If $\Delta H > T \Delta S$, the reaction is endergonic ($\Delta G > 0$)

(b) Previous work:

carboxylation of o-alkylphenyl ketone by Murakami et al.

$$O=C=O + Ph + H + G = 17.3 \text{ kcal/mol} + HO_2C + HO_2C$$

hydroamination of C-C double bond by Knowles et al.

(c) This work: addition of C-H bond to C-O double bond

Scheme 1 The photochemical approach to offset the entropic cost of endergonic intermolecular addition to an unsaturated bond.



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recently reported the hydroamination of C–C double bonds using a photocatalyst.²ⁱ It is noteworthy that this reaction is exothermic, yet still endergonic due to the large entropic cost. However, despite the significant impact of these reports, the design of photochemical approaches to drive endergonic reactions having critical entropic cost has rarely been reported. Herein, we report a new light-driven endergonic addition reaction to demonstrate that such a photochemical approach is effective at driving endergonic reactions by offsetting the entropic cost.

We examined the addition of *N*-methylamine to aromatic ketones, where the C-H bond of the methyl group on the amine adds across the unsaturated C-O bond of the ketone (Scheme 1c). Although the intramolecular Norrish-Yang-type variant of this reaction has been well-studied and applied to a wide range of synthetic targets,⁴ the intermolecular process remains elusive. Several examples of this reaction have recently been achieved *via* radical-radical coupling induced by photoredox catalysts.⁵ However, development of the reaction under photocatalyst-free conditions still poses a challenge, probably because control of the radical generation rate, which is needed for selective radical-radical coupling, is difficult in noncatalytic systems.⁶

Our study of this transformation began with the reaction of benzophenone (**1a**) with *N*-methyldiphenylamine (**2a**) in acetonitrile under irradiation by an LED lamp (365 nm). Light irradiation of the mixture in the absence of any additive provided the desired coupling product **3a** in only 10% yield, along with the formation of compound **4** and carbazole **5** (entry **1**, Table **1**). After optimization of the reaction conditions (see ESI†), we found that addition of a substoichiometric amount of base significantly increased the selectivity; the use of LiO*t*Bu (0.2 eq.) or NaO*t*Bu (0.2 eq.) was optimal for affording product **3a** in 73% and 80% yield, respectively (entries 2 and 3). Notably, further increase in the amount of base did not improve the yield (entry **4**). We assumed that MO*t*Bu assists in the generation of the α -aminoradical by deprotonation of the amine to a photoexcited ketone, at the

O Ph Ph 1a, 1.0 mmol + A Ph CH ₃ CN, rt, 2 N Ph 2a (2 eq)		tive rt, 24 h LED lamp	$e \qquad 3a \qquad i \\ Ph \qquad N \\ Ph \qquad N \\ Ph \qquad N \\ Ph \qquad N \\ Ph \qquad HO OH \qquad N \\ ED lamp \qquad Ph \qquad Ph \qquad Ph \qquad + \qquad N \\ Ph \qquad Ph \qquad + \qquad 5$		
		Yield (%)			Conversion
Entry	Base (eq.)	3a	4	5	of 1a (%)
1	None	10	81	4	100
2	LiOtBu (0.2)	73	N.D.	Trace	100
3	NaOtBu (0.2)	80	N.D.	Trace	98
4	NaOtBu (0.5)	57	N.D.	Trace	97
5^a	NaOtBu (0.2)	ND	ND	ND	11

Table 1 Addition of *N*-methylamine **2a** to benzophenone (**1a**) under photocatalyst-free conditions

^{*a*} In the absence of light-irradiation.

We examined the theoretical thermodynamics of the reaction using DFT calculations. The calculation implies that the reaction is endergonic with a ΔG value of 15.4 kcal mol⁻¹ (entry 1, Table 2). The ΔH and ΔS values were calculated to be 0.3 kcal mol⁻¹ and -51 cal mol⁻¹ K⁻¹, respectively. In general, DFT calculations overestimate entropic costs, and thus, to evaluate the entropic term more precisely, the translational entropy was corrected using the method of Whitesides.8 The corrected calculation indicated a similar thermodynamic tendency (entry 2). Based on these results, we concluded that the reaction is thermodynamically unfavorable, and the energetic cost is mainly due to entropy loss. In addition, the large negative change of the translational entropy $(\Delta S_{\text{trans}} = -24 \text{ cal mol}^{-1} \text{ K}^{-1})$ implies that the entropic cost is largely derived from the decrease of the number of molecules during the course of the reaction. In this reaction, the light energy consequently offsets such entropic cost to serve as a driving force.

To demonstrate the practical synthetic utility of this reaction, we first explored the scope of the amines in the reaction with benzophenone (Table 3). In these reactions, either LiOtBu or NaOtBu was used as the base. Amines bearing diverse functional groups, including methyl, fluoro, bromo, boryl, and alkoxycarbonyl, reacted efficiently to give the desired products in moderate to good yields (3b-3h). The yield was reduced for a secondary amine (3i). N-Methylcarbazole also reacted to produce 3j in moderate yield. Subsequently, we investigated the scope of the aromatic ketones. Electron-rich, neutral, and electron-deficient aromatic ketones all smoothly coupled with N-methyldiphenylamine to form the desired products in good to excellent yields (3k-3n). Heteroaromatic ketones such as xantone and thioxantone also underwent the coupling, albeit in lower yields (30 and 3p). The low isolated yields are partially due to gradual decomposition of the products during purification with column chromatography.

This coupling method is also adaptable to a large-scale synthesis; the reaction of **1a** and *N*,*N*-dimethylaniline on a 48 mmol scale provided 11.0 g of the coupling product **3d**. Notably, the yield was comparable with that at the 1 mmol scale by elongation of the reaction time (40 h). A double coupling reaction was also feasible; a diketone reacted at both ketone sites with both *N*-dimethylaniline (**3q**) and *N*-methyldiphenylamine (**3r**).



^{*a*} DFT calculation were performed using B3LYP-GD3(BJ)/6-311++G(d,p) with the PCM solvent model (solvent = acetonitrile). Energies were calculated at 298.15 K and 1 atm. ^{*b*} Translational entropy was corrected using the method of Whiteside.⁷

Table 3 Substrate scope^a



^{*a*} Reactions were performed with the ketone (1.0 mmol), amine (2 eq.) and base (0.2 eq.) in CH₃CN at r.t. for 24 h under UV LED lamp irradiation (365 nm). GC yields are shown, with isolated yields in parentheses. ^{*b*} NaOtBu was used as the base. ^{*c*} LiOtBu was used as the base. ^{*d*} Amine (4 eq.) and LiOtBu (0.4 eq.) were used. ^{*e*} Reaction time was 40 h.

To study the regioselectivity, we examined unsymmetrical amines having two potentially reactive sites on the nitrogen atom (Scheme 2). When *N*-ethyl-*N*-methylaniline was subjected to the optimal conditions, the reaction proceeded predominantly at the *N*-methyl group. Furthermore, in the case of *N*-benzyl-*N*-methylaniline, the addition was observed to take place exclusively at the *N*-methyl group. We assumed that this excellent regioselectivity toward the *N*-methyl group resulted from the selective generation of an α -amino radical, which would be generated by electron transfer from the amine to the photoexcited ketone, followed by deprotonation of the resulting aminium radical (Scheme 3a). Deprotonation of an aminium radical is already known to be significantly affected by stereoelectronic effects



Scheme 2 Regioselective addition of unsymmetrical amines to benzophenone (1a).



Scheme 3 (a) Plausible mechanism and (b) selective deprotonation pathway to produce the α -amino radical.



Scheme 4 Synthesis of functional π -conjugated enamines by dehydration of the aminoalcohols.

between the nitrogen center and the C–H bond.⁹ In the case of deprotonation at the *N*-ethyl or *N*-benzyl group, orbital overlap between the nitrogen and the C–H bond diminishes due to steric repulsion, resulting in the small stereoelectronic effect (Scheme 3b). Consequently, deprotonation would occur selectively at the *N*-methyl carbon.

To demonstrate the synthetic utility of the reaction, we converted the amine products to functional π -conjugated enamines (Scheme 4).¹⁰ Several aminoalcohols were smoothly transformed into the corresponding enamines simply by heating at 60 °C in the presence of molecular sieves. This method has obvious advantages over previous synthetic methods,^{10,11} such as the use of readily available *N*-methylamines and aromatic ketones as substrates, no need to use a transition-metal catalyst, and high atom efficiency.

In conclusion, we have developed a light-driven thermodynamically unfavorable addition of *N*-methylamine to aromatic ketones under photocatalyst-free conditions. Theoretical calculations indicate that light energy serves as the driving force by offsetting the entropic cost. It should be noted that such an entropic cost generally accompanies the numerous addition reactions used to assemble the building blocks to construct a product. This study demonstrates that a photochemical approach provides a powerful method to drive such entropically unfavorable reactions without requiring any driving force from chemical reagent or heat. Since previous studies of light-driven reactions mostly focused on the enthalpic term, namely endothermic reactions, we anticipate that design of light-driven uphill reactions focusing on the entropic cost will open up a distinctive reaction space in photoreaction chemistry. This method has several synthetic advantages, such as high selectivity and scalability, as well as high atom economy. Furthermore, the reaction enables a novel synthetic route to access functional enamines from easily available substrates.

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Conflicts of interest

There are no conflicts to declare.

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