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Photo-mediated [1, 3]-Carbonyl shift of β-Ketocarbonyls

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ABSTRACT

An organic amine mediated photolytic [1,3]-benzoyl migration of β-benzoyl carbonyl compounds was reported. This migration was achieved by Norrish-Yang cyclization and retro-aldol reaction under black light (365 nm) or visible light irradiation. This photolytic protocol provides an alternative approach to the synthesis of 1,5-dicarbonyl compounds. By chiral primary amine catalysis, a kinetic resolution was also developed to afford enantioenriched 1,5-dicarbonyls.

1. Introduction

We recently investigated an enamine-version de Mayo reaction using chiral primary amine catalysis (Scheme 1, I) [1]. Unfortunately, the reaction did not afford the desired de Mayo adduct **3a**, but an [1,3]-benzoyl shift product **4a** together with its further cyclic-condensation product (vide infra). Mechanistically, the rearrangement adduct **4a** was formed via a retro-aldol process following the typical carbonyl Norrish-Yang cyclization (Scheme 1, I) [2,3]. In this case, the inherent structural feature of 1,3-diketones facilitates a facile retro-aldol C-C cleavage of the Norrish-Yang cyclobutanol (Scheme 1, **II**) to give 1,5-diketones [2,3,4]. From the synthetic point of view, this Norrish-Yang cyclization and retro-aldol sequence provides a facile access to 1,5-diketones, which are recognized as versatile synthetic intermediates for their widely applications in organic synthesis [5]. Though known in carbonyl photo-processes, [2] the synthetic potential of this Norrish-Yang-retro aldol process remained surprisingly much less explored [3]. The major challenge comes from the always accompanied α- and β-cleavage competing pathways,[4,6,7] diminishing its synthetic applicability. The observation of sole-production of benzoyl-shift adduct **4a** in the presence of aminocatalyst promoted us to further investigate this reaction. Herein, we'd like to report an amine-promoted and photo-mediated protocol that complements the typical Michael addition procedure in accessing 1,5-diketones [8]. In addition, a kinetic resolution of the 1,5-ketones via an intramolecular aldol condensation has also been developed with our chiral primary amine catalysts [9,10]

2. Experimental section

2.1. Materials

The corresponding 1,3-diketones **2a**-**2u** were prepared by alkylation of the corresponding α-unsubstituted 1,3-diketone with alkyl bromide iodide [11] or addition of aldehydes to enones;[12] β-ketoesters **2v**-**2x** were prepared by alkylation of the corresponding α-unsubstituted β-ketoesters with alkyl bromide;[13] cyclic substrates **6** were prepared by direct alkylation of corresponding β-ketoesters or 1,3-diketones with activated cycloalkanes [14].

2.2. Procedure

An oven-dried 10 mL schlenk tube was charged with **2a** (0.1 mmol, 1.0 equiv) and additive. The tube was purged with a stream of nitrogen, solvent was added via syringe. The resultant mixture was degassed three times. Then the tube was placed approximately 2 cm to 15 W 365 nm LED (black light) and stirred at room temperature for given time. The reaction mixture, upon concentration, was purified directly by silica gel column to give the target products **4a** as the major product. General procedure of reactions of other substrates see SI.

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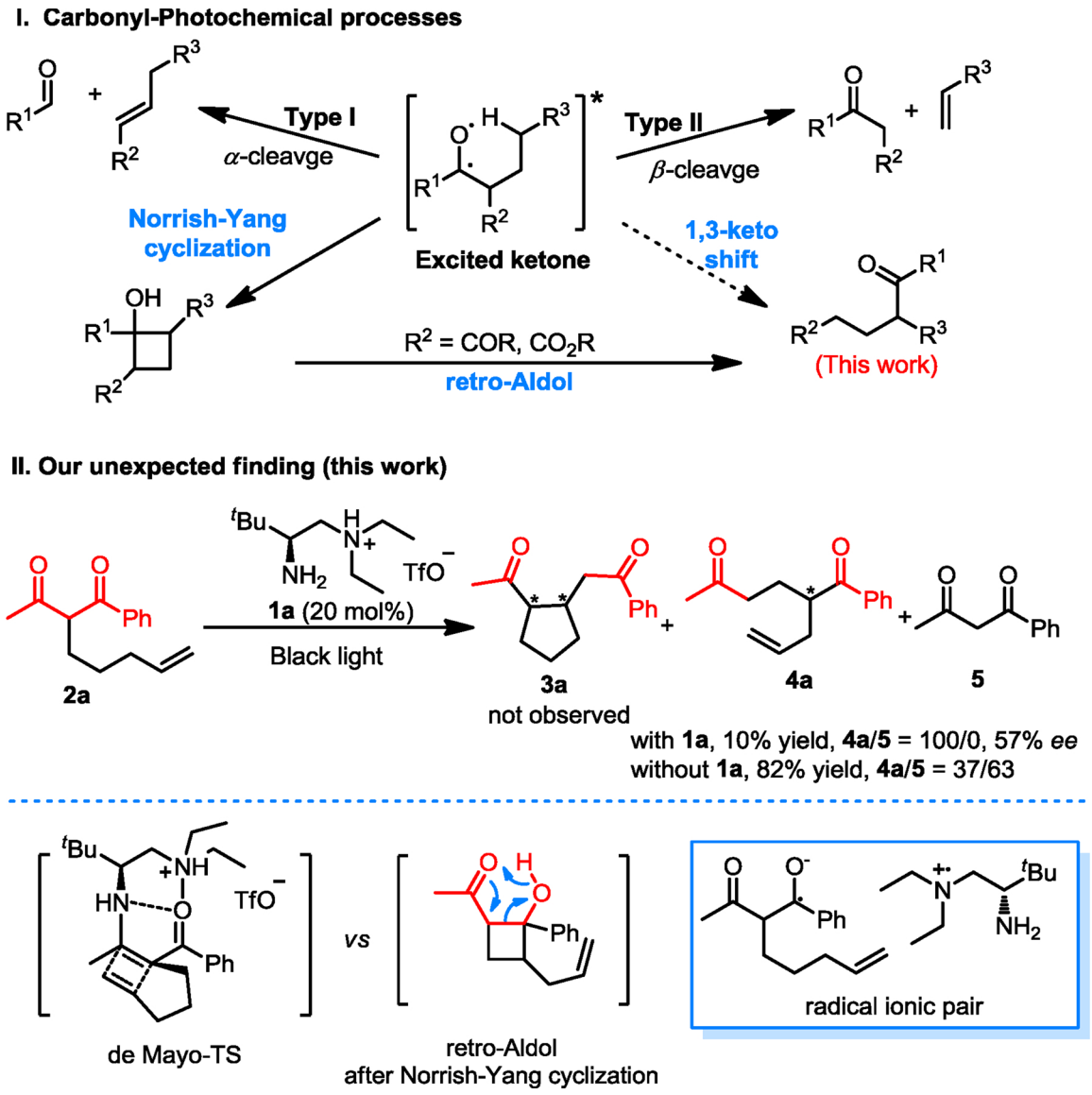


Scheme 1. Typical Carbonyl Photochemistry and our unexpected finding of a Norrich-Yang-retro Aldol process.

3. Result discussion

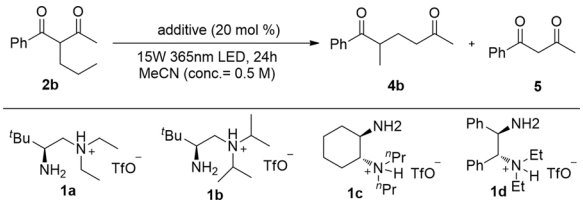
3.1. Optimization of conditions

In our initial experiments, we found the photoexcitation of **2a** in the absence of chiral primary amine **1a** led to a dealkylated **5** as the major product, via the typical Norrish Type-II process (Scheme 1, **II**). It is known that amine could retard the Norrish cleavage process by stabilizing the excited carbonyl in the form of radical ion pair (as shown in Scheme 1, **II**) [15]. This result promoted us to further optimize the reaction by screening different base in this photochemical process (Table 1). Under the irradiation of 365 nm LED, the reaction afforded mainly dealkylated adduct **5** together with a minor [1,3]-acyl shifted adduct **4a** (Table 1, entry 1) in the absence of any additive. The addition of both inorganic acid and base didn't lead to any improvement (Table 1, entries 2–5). Protonated diamines **1a**-**1d** as catalysts result in extremely low yields, although no dealkylated adduct **5** was observed (Table 1, entries 6–10). In these cases, notable enantioselectivity was observed, and this was later ascribed to a following-up kinetic resolution process (see Scheme 4). The screening of other organic base led to the identification of quinuclidine as the optimal additive. The use of one equivalent quinuclidine in *p*-xylene gave 64 % yield of [1,3]-benzyl shifted adduct **4b** as the major product (Table 1, entries 11–15). Under this condition, minor dealkylated product **5** was still isolated and this compound in fact also served as the starting material in preparing **2a**, thus could be recycled and reused.

3.2. Substrate scope

With optimized conditions in hand, we investigated the substrate

Table 1
Optimization of Reaction Conditions [a].



Entry	additive	Yield of 4b (%)	Yield of 5 (%)
1	No	30	52
2	K_2CO_3	31	53
3	NaOH	40	51
4	$FeBr_2$	25	30
5	$InCl_2$	35	34
6	1a	10 (58 % *ee*)	0
7	1a[b]	12 (51 % *ee*)	0
8	1b	7 (50 % *ee*)	0
9	1c	12 (1% ee)	7
10	1d	8 (4% *ee*)	3
11	DABCO	40	42
12	Quinuclidine	52	43
13[c]	Quinuclidine	55	40
14[d]	Quinuclidine	61	36
15[e]	Quinuclidine	64	34

[a] Reactions were performed at room temperature in 0.2 mL MeCN with **b2** (0.1 mmol), additive (20 mol %) under 15 W 365 nm LED, N_2, 24 h. Yield of isolated product.
[b] $Tf2N^-$ instead of TfO^-.
[c] 1.0 eq additive.
[d] 1.0 eq additive, in *p*-xylene.
[e] 1.0 eq additive, in *p*-xylene, conc. = 0.3 M.

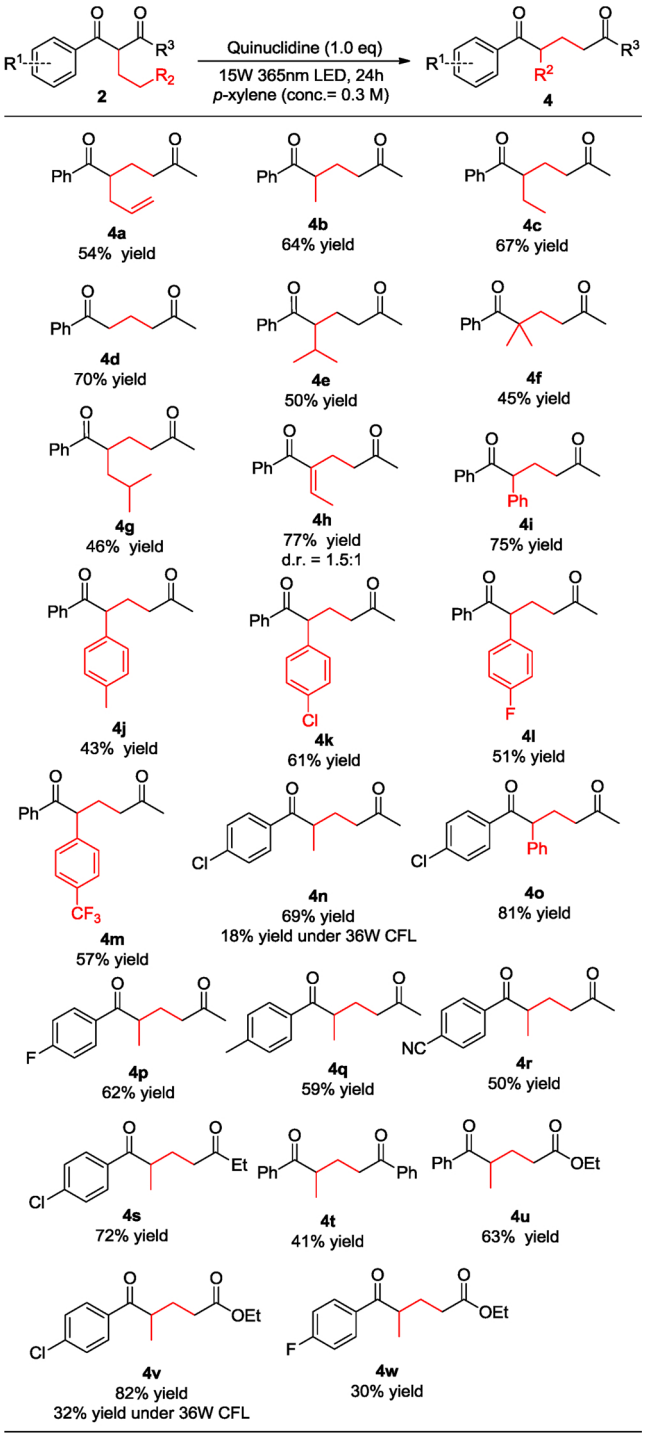
scopes of this reaction (Schemes 2 and 3). 1,3-Diketones bearing different 2-alkyl (R^2 = alkyl) groups were well tolerated to give the benzoyl-shifted adducts in moderate to good yields (**4a-4h**). When 2-phenethyl substituted 1,3-diketones **2** were used (R^2 = aryl), the reaction afforded *α*-aryl substituted 1,5-diketones (**4i-4m**) in good yields. Substitutions on the benzoyl moiety (R^1) with either electron-withdrawing or electron-donating group were both tolerated (**4p-4s**). Besides methyl ketones (R^3), larger ethyl ketone (**4s**) and phenyl ketone (**4t**) as well as esters (**4u-4w**) could also be applied with moderate to good reactivity.

When 2-cycloalkanyl 1,3-ketocarbonyls were examined, the reaction showed better activity compared with its linear acyclic counterparts (Scheme 3, 12 h vs 24 h). In these cases, di-substituted ring compounds were obtained in good yields with high diastereoselectivity. Both cyclopentanyl and cyclohexanyl ring could be applied and the diastereoselectivity was determined to be *anti-* for both cases [16].

A concentration-depended red-shift of the ketocarbonyls were observed in UV–vis spectra (see SI, Figure S1 and S2) [17]. At reaction concentrations, significant absorption above 360 nm were clearly noted (e.g. **2n**) and some even shifted to the visible light range (e.g. **4n**, **4v** and **7e**). In the latter cases, conversion to the desired product could be observed under visible light irradiation (Schemes 2 and 3).

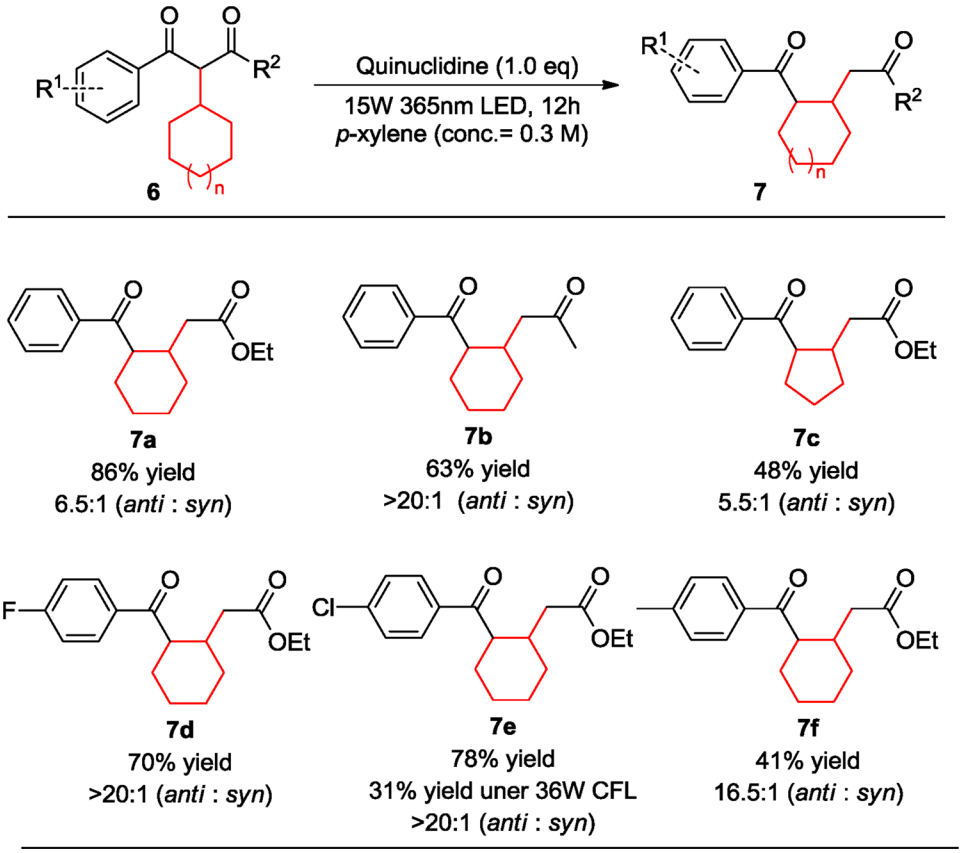
3.3. Further transformation: kinetic resolution

We further explored a kinetic resolution protocol to access chiral 1,5-diketones by taking advantage of chiral primary amine catalyzed



Scheme 2. Substrate scope of linear ketones[a].
[a]Reactions were performed at room temperature in 0.33 mL *p*-xylene with **2** (0.1 mmol), quinuclidine (0.1 mmol) under 15 W 365 nm LED, N_2, 24 h. Yield of isolated product.

intramolecular aldol condensation [9,10]. Chiral primary amines catalyst such as **1a-1d** have been widely applied in a number of direct aldol reactions, [9d] but their application in kinetic resolution remains



Scheme 3. 1,3-Benzoyl shift onto cyclic compounds***a***.
[a]Reactions were performed at room temperature in 0.33 mL *p*-xylene with **6** (0.1 mmol), quinuclidine (0.1 mmol) under 15 W 365 nm LED, N_2, 12 h. Yield of isolated product

underdeveloped. After a brief screening, **1b** was identified as the optimal catalyst and the kinetic resolution worked favorably in diethyl ether (conc. = 0.5 M) under -10 ℃ to give enantio-enriched 1,5-diketone in 91 % *ee*. The resolution factor *s* was determined to be 15 in this case (**4b**) (Scheme 4). Good kinetic resolution was also achieved in several other cases (Scheme 4). Unfortunately, the use of cylic 1,5-diketone such as **7b** showed rather poor resolution. The stereoncontrol with the protonated N—H bonding, in consistence of our previous studies, [9,10] could be invoked to account for the stereoselectivity and this was further verified by DFT calculations.

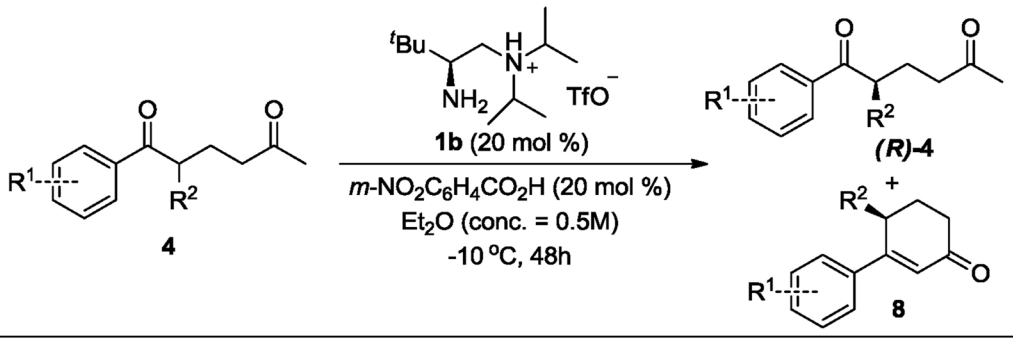
3.4. Discussion

Mechanistically, the role of amine in this 1,3-carbonyl shift is quite intriguing particularly regarding the control of chemoselectivity. It's known that amine could stabilize the excited carbonyl in the form of radical ion pair (Scheme 1) and facilitate the formation of 1,4-biradical (e.g. **9**) via 1,5-H abstraction [15]. In the absence of amine, the forming biradical intermediate **9** would mainly exist in chair formations due to the favored intramolecular H-bonding (Scheme 5, **I**). Chair conformation **9a** was disfavored over **9b** with the latter bearing an equatorial alkyl radical, which would facilitate *β*-cleavage instead of the more strained cyclization to form cyclobutane. This conformational bias may explain the dominant formation of dealkylated product (e.g. **5**) via *β*-cleavage (Scheme 1, **II** and Table 1, entry 1). On the other hand, the presence of amine may interrupt the intramolecular H-bonding via strong acid-base interaction. The strong basic and bulky nature of quinuclidine may enforce this interruption and the acyclic biradical **10** may now prefer a conformer **10a** due to steric effect, which favors the cyclobutane formation pathway (Scheme 5, **II**).

The stereoselectivity in the kinetic resolution could be accounted by a H-bonding mode with our chiral primary amine catalyst [15,18]. The favored S-selective transition state **Ts-1a** features a strong H-bonding between protonated N—H and carbonyl O (1.59 Å in **Ts-1a** vs 1.69 Å **in Ts-1b**) and diminishing close contact between C—H of isopropyl and one C—H of methylene (Fig. 1, **Ts-1b**, red ellipse).

4. Conclusions

In conclusion, we have developed an amine mediated [1,3]-



8	(R)-4	Conversion	Recovery	ee (8)	ee ((R)-4)	s factor
8b	(R)-4b	55%	42%	70%	91%	15
8c	(R)-4c	58%	42%	65%	90%	17
8n	(R)-4n	54%	45%	75%	90%	20
8p	(R)-4p	45%	51%	80%	73%	16
8q	(R)-4q	39%[b]	49%[b]	87%	77%	22

Scheme 4. Kinetic resolution of 1,5-diketones by chiral primary amine catalysis[a].
[a]Reactions were performed in diethyl ether with rac-**4** (0.1 mmol), **1b** (0.02 mmol) and *m*-nitrobenzoic acid (0.02 mmol) at −10 °C, N_2. Yield of isolated product.
[b]72 h.

carbonyl migration of *β*-benzoyl carbonyl compounds under photolytic conditions. The reaction undergoes a sequence of Norrish-Yang cyclization and retro-aldol process to give 1,5-diketones or *δ*-benzoyl esters. This study enlarged the scope of Norrish-Yang reaction to enable efficient synthesis of 1,5-dicarbonyls.

Author statements

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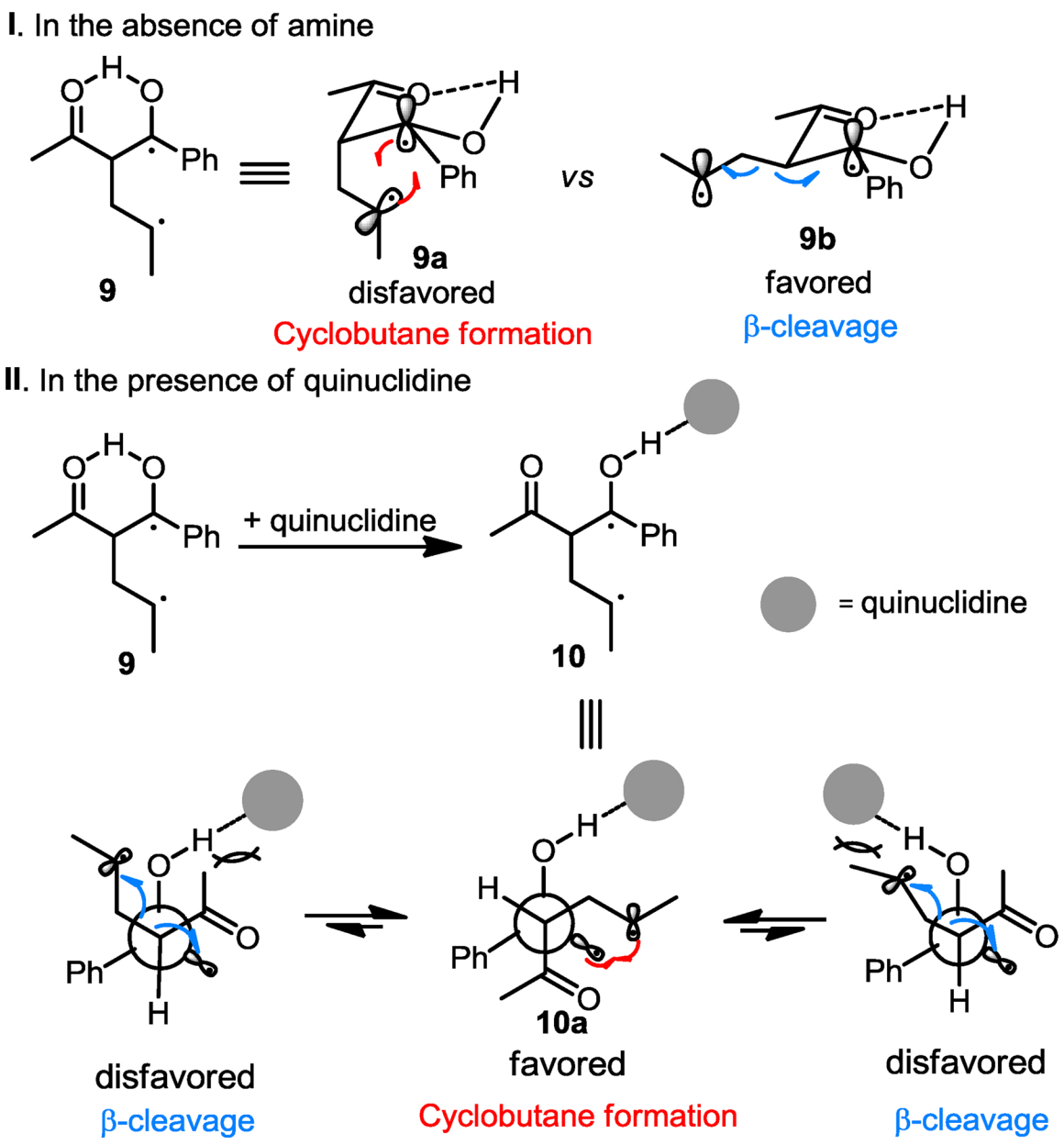

Scheme 5. Conformational analysis in the absence (I) and presence of quinuclidine.

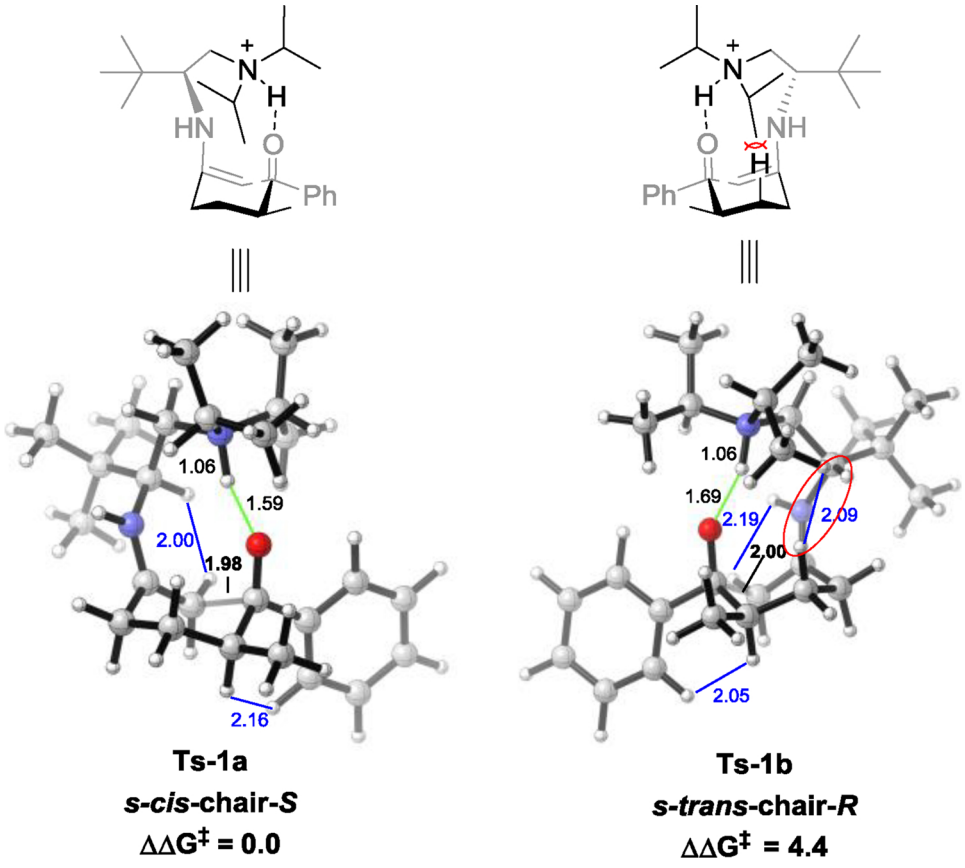

Fig. 1. Calculated transition states in kinetic resolution.[a]
[a]Relative free energies of activation are given in kcal/mol. Interatomic distances are denoted in Å. The close H–H contacts (< 2.2 Å) are labeled in blue.

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Declaration of Competing Interest

We declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jphotochem.2020.112553.

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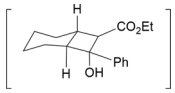
[16] The anti-selectivity can be explained by considering the following Norrich-Yang cyclization intermediate. 

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