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RESEARCH ARTICLE

Visible-Light-Induced Synthesis of 1,2,3,4-Tetrahydroquinolines via Formal [4+2] Cycloaddition of Acyclic α,β-Unsaturated Amides and Imides with *N*,*N*-Dialkylanilines

Kennosuke Itoh*, Shun-ichi Nagao, Ken Tokunaga, Shigeto Hirayama, Fumika Karaki, Takaaki Mizuguchi, Kenichiro Nagai, Noriko Sato, Mitsuaki Suzuki, Masashi Hashimoto and Hideaki Fujii*

Abstract: 1,2,3,4-Tetrahydroquinolines should be applicable to the development of novel pharmaceutical agents. We report a facile synthesis of 1,2,3,4-tetrahydroquinolines that was achieved by a photo-induced formal [4+2] cycloaddition reaction of acyclic α,β-unsaturated amides and imides with *N*,*N*-dialkylanilines under visible-light irradiation where a novel Ir(III) complex photo-sensitizer, a thiourea, and an oxidant act cooperatively in promoting the reaction. The photo-reaction enables the synthesis of a wide variety of 1,2,3,4-tetrahydroquinolines while controlling *trans*/*cis* diastereoselectivity (>99:1) and constructing contiguous stereogenic centers. A chemoselective cleavage of an acyclic imide auxiliary is demonstrated.

Introduction

1,2,3,4-Tetrahydroquinoline (1,2,3,4-THQ) is a promising scaffold for drug discovery.[1] A number of 1,2,3,4-THQs possessing an affinity for biological systems have been developed in medicinal chemistry.[2] We were able to discover a 1,2,3,4-THQ framework in the structure of naturally occurring molecules which showed a wide variety of biological activities.[3] Because of the significance with biological relevance of 1,2,3,4-THQs, a number of non-photochemical reactions for construction of a 1,2,3,4-THQ skelton[4] have been developed such as formal [4+2] cycloaddition reactions of maleimides and a very few acyclic α,β-unsaturated compounds with *N,N*-dialkylanilines,[5] Povarov reaction,[6] metal-mediated reactions,[7] Brønsted acid-catalyzed reactions,[8] secondary amine-catalyzed reactions,[9] bifunctional amine-thiourea-catalyzed reactions,[10] iodonium ion-promoted reactions,[11] cyclopropane ring-opening reactions,[12] *o*-azaxylylene-mediated reactions,[13] intramolecular cyclization reactions of nitrogen-nucleophiles to indoles and oxindoles,[14] and transformation reactions of quinolines.[15,16] Besides, three types of straightforward photochemical reactions afford the syntheses of 1,2,3,4-THQs. Among them, photochemically promoted aza-Diels-Alder type reactions [17] and the photo-induced aerobic decarboxylative Povarov reaction[18] have been developed in recent years. Photo-induced formal [4+2] cycloaddition reactions of α,β-unsaturated carbonyl compounds with *N*,*N*-dialkylanilines have long been studied, but the most commonly reported reactions involved the use of maleimides as a reaction partner of *N*,*N*-dialkylanilines.[19] Hence, it has been difficult to introduce different types of substituents in the resulting 1,2,3,4-THQs and to produce the *cis*-stereoisomer. A few examples of the reaction using cyclic α,β-unsaturated ketones, cyclic lactones, and cyclic amides instead of maleimides have been reported, however, the reactions are limited in terms of poor substrate generality and low yield of 1,2,3,4-THQs.[20]

The reaction of acyclic α,β-unsaturated compounds with *N*,*N*-dialkylanilines has the possibility of enabling syntheses of 1,2,3,4-THQs possessing a wide variety of substituents with control of *trans*/*cis* diastereoselectivity and enantioselectivity. However, there are very few reports of the photo-induced and the non-photo-induced reactions using acyclic α,β-unsaturated compounds, *e.g.*, arylidene malononitrile,[21] dialkyl fumarate,[5b,7d,20d] and 1-(2-alkenoyl)-3,5-dimethylpyrazole.[22] Among the three types of acyclic α,β-unsaturated compounds, 1-(2-alkenoyl)-3,5-dimethylpyrazole has utilized for the reaction of *N*,*N*-dialkylaniline to give 1,2,3,4-THQs where a bidentate chelation complex of chiral Lewis acid, (*R*,*R*)-DBFOX/Ph•Ni(II)[23] with 1-(2-alkenoyl)-3,5-dimethylpyrazole serves as a photocatalyst,[22] however, only two reactions have been demonstrated. As a result, *trans*/*cis* diastereoselectivities are high without revealing relative configurations, however, enantiomeric excesses are almost zero.

In Scheme 1, we depict a proposed mechanism for the photo-induced formal [4+2] cycloaddition reaction of α,β-unsaturated compounds with *N*,*N*-dialkylanilines **I**.[24] The photo-sensitizer (Sens.) absorbs light to generate the excited state photo-sensitizer (*Sens.) which is subsequently quenched by *N*,*N*-dialkylaniline **I** via single electron transfer (SET) to give the amine

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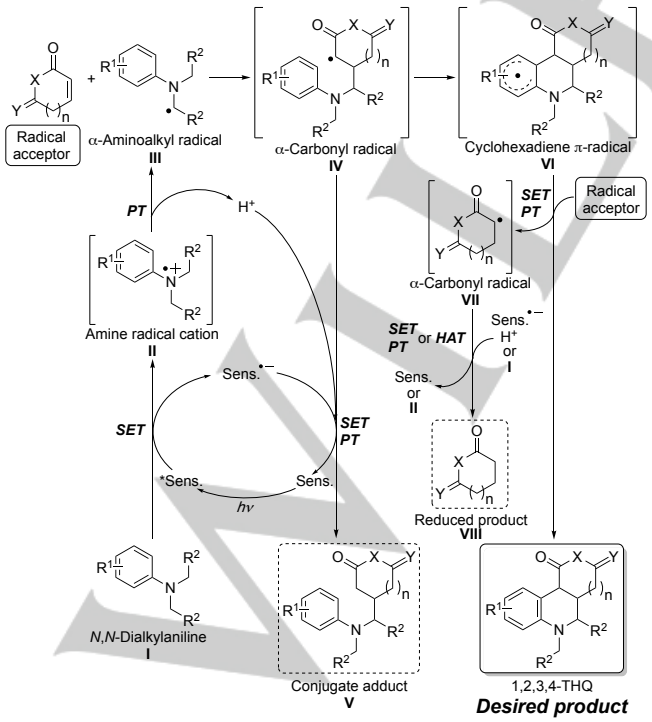
10.1002/chem.202004186

radical cation **II** and the reduced photo-sensitizer (Sens.•−). The amine radical cation **II** induces proton transfer (PT) to provide the α-aminoalkyl radical **III**. The resulting α-aminoalkyl radical **III** reacts with the radical acceptor through radical conjugate addition (RCA) to afford the α-carbonyl radical **IV** which follows two different fates. One is formation of the conjugate adduct **V** along with the re-generated Sens. where the α-carbonyl radical **IV** is subject to SET by reaction of Sens.•− to give the corresponding enolate which subsequently reacts with the amine radical cation **II** via PT. The other pathway forms the desired 1,2,3,4-THQ along with the reduced product **VIII**. The α-carbonyl radical **IV** undergoes radical cyclization to generate the cyclohexadiene π-radical **VI** which subsequently reacts with the radical acceptor via SET followed by PT or *N*,*N*-dialkylanilines **I** via hydrogen atom transfer (HAT). Eventually, the cyclohexadiene π-radical **VI** completes aromatization to give 1,2,3,4-THQ. The sequential radical cyclization-aromatization is termed homolytic aromatic substitution (HAS).[25,26] To complete HAS, the cyclohexadiene π-radical **VI** must be oxidized by the radical acceptor or an oxidizing additive[20a,20b] to form 1,2,3,4-THQ along with α-carbonyl radical **VII** via SET followed by PT. The α-carbonyl radical **VII** reacts with Sens.•− and a proton to give the reduced product **VIII** and Sens.[19b,19e,19g] There is a possibility that the α-carbonyl radical **VII** abstracts hydrogen of *N*,*N*-dialkylanilines **I** to afford the reduced product **VIII** and α-aminoalkyl radical **III**.[20b,20f,20g] Formation of the reduced product **VIII** is inevitable and sacrifices the yield of 1,2,3,4-THQ.[20g] Intrinsically, LUMO and SOMO energy levels of maleimides and the corresponding α-carbonyl radical **IV** are close to the SOMO and HOMO energy levels of the α-aminoalkyl radical **III** and aromatic ring, respectively. Additionally, an excess amount of maleimides is necessary to obtain 1,2,3,4-THQs unless molecular oxygen is used as an oxidizer.[15] Therefore, maleimides are allowed to be utilized as a radical acceptor without critical problems.



Scheme 1. An overview of the photo-induced formal [4+2] cycloaddition of cyclic α,β-unsaturated compounds with *N*,*N*-dialkylanilines.

We envisioned that a photo-induced formal [4+2] cycloaddition of acyclic α,β-unsaturated compounds with *N*,*N*-dialkylanilines would be developed by carrying out the following points: (i) Using a novel Ir(III) complex photo-sensitizer (Ir(III) complex)[27], a facile formation of the α-aminoalkyl radical **III** and a disturbing formation of the conjugate adduct **V** would be achieved by an excellent oxidizing ability of an excited Ir(III) complex (corresponding to *Sens.) and a suitable reactivity of a Ir(II) complex (corresponding to Sens.•−); (ii) Using thioureas, LUMO and SOMO energy levels of the acyclic α,β-unsaturated carbonyl compound and the α-carbonyl radical **IV** would be controlled by a hydrogen-bonding interaction to make reaction pathways converge with formation of the cyclohexadiene π-radical **VI** with control of *trans*/*cis* diastereoselectivity and enantioselectivity; (iii) Using azo compounds, a facile aromatization of the cyclohexadiene π-radical **VI** would be accomplished and precluded formation of the reduced product **VIII** by oxidation.

Herein, we present the first photo-induced formal [4+2] cycloaddition reaction of a wide variety of acyclic α,β-unsaturated compounds with *N*,*N*-dialkylanilines to give 1,2,3,4-THQs in a highly diastereoselective manner. The cooperative action of a novel Ir(III) complex, a thiourea, and an azo compound is the key to the success of this reaction.

Results and Discussion

We chose 1-crotonoyl-3,5-dimethylpyrazole (**1a**) as the acyclic α,β-unsaturated carbonyl compound, because **1a** was known as a good radical accepter (Table 1).[22,28] The reaction of 1-crotonoyl-3,5-dimethylpyrazole (**1a**) with *N*,*N*-dimethylaniline (**2**) did not occur in the absence of an Ir(III) complex under visible-light-irradiation (entry 1). The first attempt to use Ir(III) complex **4a**, however, afforded a slight amount of 1,2,3,4-THQ **5aa** with a poor ratio of 1,2,3,4-THQ **5aa** to conjugate adduct **6** and high diastereomeric ratio (d.r.) (entry 2). We could not detect the reduced product, 1-butanoyl-3,5-dimethylpyrazole (**7**), because a number of by-products interrupted spectroscopic identification for formation of **7** even after attempting chromatographic isolation. Based on these results, we decided to add thiourea **3a** as a Brønsted acid,[29] because **3a** has been recognized as a good hydrogen-bonding donor in the amine conjugate addition to facilitate the reaction rate by controlling LUMO energy levels of 1-(2-alkenoyl)-3,5-dimethylpyrazole (**1a**).[30] In our photochemical reaction, the use of thiourea **3a** made a significant impact not only by enhancing the reaction rate, but also favoring formation of 1,2,3,4-THQ **5aa** (entry 3). Since the reaction of 1-crotonoyl-3,5-dimethylpyrazole (**1a**) with *N*,*N*-dimethylaniline (**2**) occurred in the presence of thiourea **3a** and Ir(III) complex **4a**, we screened Ir(III) complexes. No reaction was induced when tris(2-phenylpyridine)iridium(III) (**4b**) was used (entry 4). Iridium(III) complex **4c,** having electron-withdrawing methoxycarbonyl groups in the bipyridine ligand, could not promote the reaction (entry 5). Using iridium(III) complex **4d** with the electron-donating

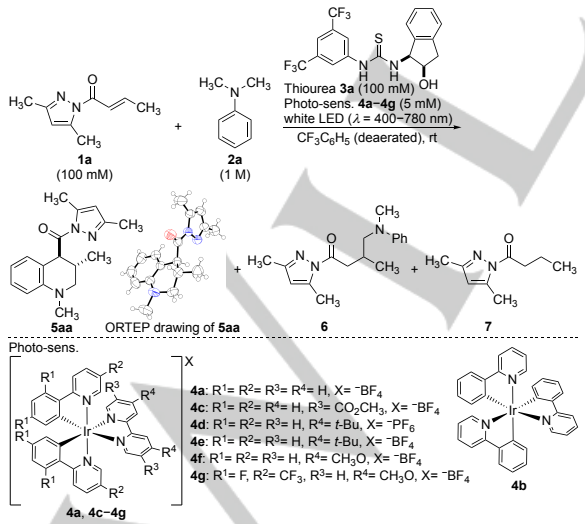
10.1002/chem.202004186

tert-butyl group in the bipyridine ligand gave results comparable with entry 3 (entry 6). Using Ir(III) complex **4e,** possessing a different counter anion from Ir(III) complex **4d**, slightly decreased the yield and d.r. of 1,2,3,4-THQ **5aa** (entry 7). In the presence of Ir(III) complex **4f** possessing an electron-donating methoxy group, the reaction occurred cleanly and led to identification of 1,2,3,4-THQ **5aa**, conjugate adduct **6**, and the reduced product **7** (entry 8). We designed and synthesized a novel Ir(III) complex **4g** having fluoro and trifluoromethyl groups in the phenyl pyridine ligand (entry 9). The introduction of the fluorine group into phenyl pyridine ligand was predicted to diminish the radiative rate constant and spin-orbit coupling strength, resulting in an extension in triplet lifetime of Ir(III) complex **4g**, which would increase the efficiency of SET from *N,N*-dimethylaniline (**2**) to the photo-excited **4g**.[31] Consequently, formation of the reduced product **7** was not observed, and besides, the yield of 1,2,3,4-THQ **5aa** and diastereomeric ratio were the best by using Ir(III) complex **4g**.

Solvents affected the reaction efficiency and the product ratio of 1,2,3,4-THQ **5aa** to conjugate adduct **6** (see Supporting Information (SI)). The reaction did not occur in aerated solutions, suggesting that the reaction proceeded through the triplet excited state of reagents.

The relative configurations of the major isomer and the minor isomer of 1,2,3,4-THQ **5aa** were determined by X-ray crystallographic analyses[32] and NMR analyses to reveal 3,4-*trans* and 3,4-*cis*, respectively. Therefore, the radical conjugate addition (RCA) followed by homolytic aromatic substitution (HAS) occurred in a *syn*-selective manner to give the 3,4-*trans* isomer predominantly. Enantiomeric excesses of 1,2,3,4-THQ **5aa** in Table 1 were almost zero. The structure of the novel Ir(III) complex **4g** was confirmed by X-ray crystallographic analyses[32] and NMR analyses (Figure 1 and SI).

Table 1: 1-Crotonoyl-3,5-dimethylpyrazole as a radical acceptor in the presence of Ir (III) complex photo-sensitizers and a thiourea.



entry	photo-sens.	**3a**	time [h]	yield [%] (**5aa**:**6**)[a],[b]	d.r. of **5aa** (*trans*:*cis*)[c]
1	none	none	43	0	–
2	**4a**	none	111	9 (67:33)	97:3
3	**4a**	yes	46	31 (91:9)	96:4
4	**4b**	yes	24	0	–
5	**4c**	yes	37	0	–
6	**4d**	yes	23	38 (95:5)	93:7
7	**4e**	yes	17	29 (91:9)	92:8
8	**4f**	yes	23	38 (94:6)[d]	94:6
9	***4g***	***yes***	***23***	***38 (96:4)***	***96:4***

[a] Yield of **5aa**. [b] Ratio of **5a** and **6** in the crude mixture was determined by ^{1}H NMR. [c] Determined by ^{1}H NMR of the crude mixture. [d] **7** was isolated in 50% yield.

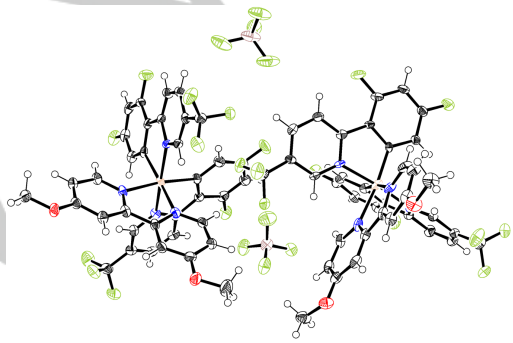


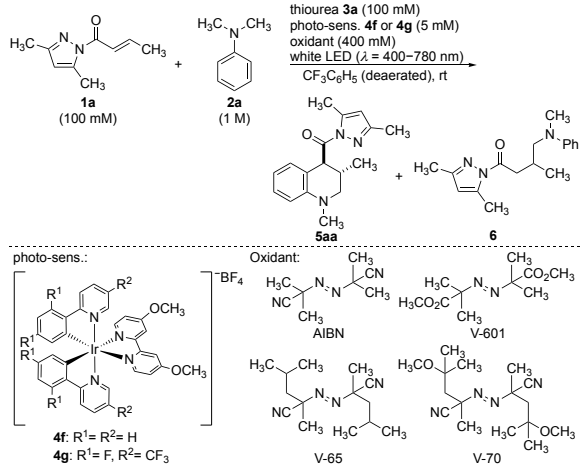
Figure 1. ORTEP drawing of Ir(III) complex **4g**: All disordered carbon atoms, a solvent, and an oxygen of crystal water were omitted for clarify.

We next added an azo compound to prevent the production of the reduced product **7** and to concomitantly promote the oxidation of the cyclohexadiene π-radical, because 2,2'-azobis(isobutyronitrile) (AIBN) is known to be a good oxidizing agent for the cyclohexadiene π-radical (Table 2).[24-26] Iridium(III) complex **4f** was used for the evaluation of azo compounds, because **4f** could be prepared much easier than Ir(III) complex **4g**. Contrary to expectations, AIBN did not work well in our reaction (entry 1). After the investigation with other azo compounds such as V-601, V-65, and V-70 (entries 2−4), we found that V-70 was the optimal oxidant (entry 4). Reducing the amount of V-70 by half (200 mM), the yield of 1,2,3,4-THQ **5aa** was decreased to 40% without affecting the product ratio of **5aa** to conjugate adduct **6** and d.r. of **5aa**. Finally, we observed that the combined use of V-70 and Ir(III) complex **4g** gave the best result (entry 5). Various types of oxidants, *e.g.*, acetone,[20b] 1,4-benzoquinone, methyl viologen, electron-deficient alkenes, and potassium persulfate did not play a role (see SI). We confirmed that the reaction did not occur in the absence of Ir(III) complex; a gas was evolved without forming 1,2,3,4-THQ **5aa** (entry 6). The gas would be nitrogen gas evolved by decomposition of V-70 to generate a carbon radical. Hence, we concluded that V-70 could not act as a radical initiator in the reaction. The diastereomeric ratio of 1,2,3,4-THQ **5aa** was

10.1002/chem.202004186

comparable whether V-70 was added or not. Enantiomeric excesses of 1,2,3,4-THQ **5aa** in Table 2 were almost zero.

Table 2: Evaluation of azo compounds.

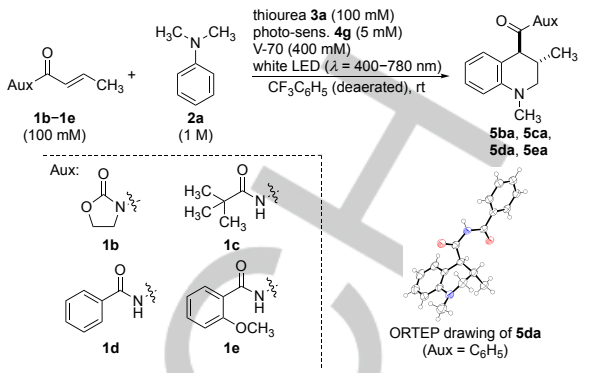


entry	photo-sens.	oxidant	time [h]	yield [%] (**5aa**:**6**)[a],[b]	d.r. of **5aa** (*trans*:*cis*)[c]
1	**4f**	AIBN	70	21 (98:2)	98:2
2	**4f**	V-601	23	33 (97:3)	98:2
3	**4f**	V-65	47	39 (96:4)	97:3
4	**4f**	V-70	46	56 (97:3)	98:2
5	***4g***	***V-70***	***70***	***64 (94:6)***	***94:6***
6	none	V-70	23	0	–

[a] Yield of **5aa**. [b] Ratio of **5a** and **6** in the crude mixture was determined by ^{1}H NMR. [c] Determined by ^{1}H NMR of the crude mixture.

With the optimal reaction conditions in hand, we evaluated several acyclic α,β-unsaturated compounds including different auxiliaries, *e.g.*, 2-oxazolidinone **1b**,[33] *tert*-butyl amide **1c**,[34] benzamide **1d**,[35] and 2-methoxybenzamide **1e**[36] (Table 3). All reactions progressed in the exclusive formation of 1,2,3,4-THQs **5ba**–**5ea** with excellent diastereoselectivities. The yields of 1,2,3,4-THQs **5ba** and **5ca** were low (entries 1 and 2), however, those of 1,2,3,4-THQs **5da** and **5ea** were moderate (entries 3 and 4). Enantiomeric excesses of 1,2,3,4-THQs **5ba**–**5ea** were low. Among them, 1,2,3,4-THQs **5ea** was obtained in moderate yield with 12% *ee* (entry 4). Finally, we clarified α,β-unsaturated imide **1e** as the suitable radical acceptor. We succeeded in X-ray crystallographic analysis of 1,2,3,4-THQ **5da** which was the 3,4-*trans* isomer.[32]

Table 3: Evaluation of auxiliaries.



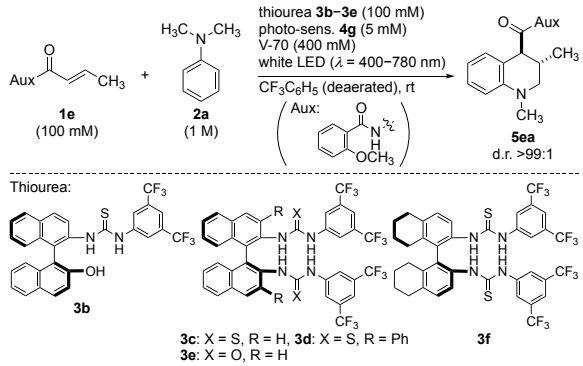
entry	alkene	time [h]	yield [%][a]	d.r. (*trans*:*cis*)[b]
1	**1b**	70	35 (**5ba**)	>99:1
2	**1c**	70	22 (**5ca**)	>99:1
3	**1d**	43	60 (**5da**)	>99:1
4	***1e***	***43***	***60 (5ea)***	***>99:1***[c]

[a] Isolated yield. [b] Determined by ^{1}H NMR of the crude mixture. [c] *Ee* of **5ea** was 12%.

Next, we synthesized several chiral thioureas to exert enhanced enantioselectivity (Table 4).[37] Thiourea **3b**, having the ((*S*)-2-amino-(1,10-binaphthalen)-2-ol) (NOBIN)[37] scaffold, was not effective for promoting the reaction (entry 1). The reaction in the presence of chiral thiourea **3c** having a (*S*)-1,1'-binaphthyl-2,2'-diamine (BINAM) backbone afforded 1,2,3,4-THQ **5ea** in good yield with 15% *ee* (entry 2). We synthesized a novel thiourea **3d** possessing phenyl groups on the 3,3'-positions of BINAM backbone which was expected to shield one enantioface of α,β-unsaturated imide **1e** (entry 3). Contrary to expectations, the reaction was decelerated and *ee* was decreased. Adding chiral urea **3e**[38] was not effective in proceeding with the reaction because of the poor solubility of **3e** (entry 4). Using thiourea **3f** having 5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diamine (H8-BINAM), the reaction rate was decreased, but *ee* was the same as entry 2 (entry 5). Other chiral thioureas and achiral thiourea, *i.e.*, 1,3-bis[3,5-bis(trifluoromethyl)phenyl]urea[39] possessing high acidity of the NH proton were not effective (see SI). Finally, chiral thiourea **3c** derived from BINAM induced the best *ee*, even though the outcome still had plenty of room for improvement. Hence, we concluded that a highly enantioselective reaction could be achieved by reducing the rotatability of carbon-nitrogen bonds of chiral thioureas. Consequently, we directed toward establishing the formal [4+2] cycloaddition reaction under achiral reaction conditions. We also assessed the reaction of a cyclic α,β-unsaturated carbonyl compound, *N*-phenylmaleimide with *N*,*N*-dimethyl-4-methylaniline (**2b**) to give the corresponding 1,2,3,4-THQ in 72% yield even in the absence of thiourea (see SI). Hence, we were truly convinced that the thiourea was indispensable to promote the reaction of acyclic α,β-unsaturated amides and imides.

10.1002/chem.202004186

Table 4: Evaluation of chiral thiourea derivatives.

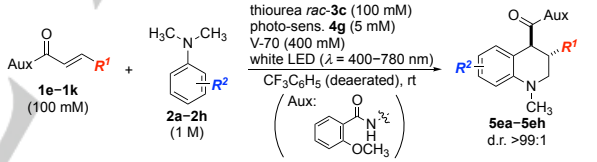


entry	thiourea	time [h]	yield [%][a]	*ee* [%][b]
1	**3b**	48	3]	7
2	***3c***	***48***	***65***	***15***
3	**3d**	48	24	10
4	**3e**	48	trace	–
5	**3f**	48	20	15

[a] Isolated yield. [b] Determined by chiral HPLC.

We decided to use racemic thiourea **3c** (*rac*-**3c**) for exploring the substrate scope (Table 5). We evaluated substituents at the β-position of α,β-unsaturated imides **1e**–**1k** (Table 5(i)). The reaction using thiourea *rac*-**3c** demonstrated comparable results with a chiral version depicted in entry 2, Table 4. The yields of 1,2,3,4-THQs **5ea**–**5ha** possessing different functional groups such as methyl, isobutyl, trifluoromethyl, and phenyl groups were comparable with each other. The rate of reaction was affected by size, electron-donating and electron-withdrawing abilities of substituents at the β-position of α,β-unsaturated imides. The *p*-fluoro group of the benzene ring at the β-position of α,β-unsaturated imide **1i** would increase electrophilicity, which appeared to accelerate the conjugate addition step. However, formation of by-products of unknown structure compromised the yield of 1,2,3,4-THQ **5ia**, which might be due to radical *ipso*-substitution of the carbon-fluorine bond.[40] Alternatively, an electron-donating *p*-methoxy and 3-furyl group would reduce electrophilicity of α,β-unsaturated imides **1j** and **1k** and caused formation of a number of by-products to decrease the yield of 1,2,3,4-THQs **5ja** and **5kb**. Several *N*,*N*-dimethylanilines **2b**–**2f** having electron-donating and electron-withdrawing substituents at the *para*-position on the benzene ring were evaluated (Table 5(ii)). *N*,*N*-Dimethyl-4-methylaniline (**2b**) was a particularly good substrate which reacted with α,β-unsaturated imides **1e** and **1g** to give 1,2,3,4-THQs **5ea** and **5gb** in good to excellent yields. Other *N*,*N*-dimethylanilines possessing electron-donating substituents such as benzyl and methoxy groups prolonged the reaction times and reduced the yields of 1,2,3,4-THQs **5ec**, **5ed**, and **5gd**. Electron-withdrawing substituents such as fluoro and bromo groups of 4-fluoro-*N*,*N*-dimethylaniline **2e** and 4-bromo-*N*,*N*-dimethylaniline **2f** slightly improved the yields of 1,2,3,4-THQs **5ee** and **5ef** along with decreasing the rates of the reactions. According to detailed kinetic studies, acidity of the *N*-methyl proton of amine radical cations is a very important factor toward facile formation of α-aminoalkyl radicals.[41] Hence, electron-withdrawing 4-fluoro and 4-bromo groups would increase acidity of the *N*-methyl proton of amine radical cations, enabling the facile formation of α-aminoalkyl radicals. Consequently, increasing the lability of the *N*-methyl proton would contribute to acceleration of the radical conjugate addition reaction, thereby increasing the yield of 1,2,3,4-THQs **5ee** and **5ef**. In contrast, electron-withdrawing 4-fluoro and 4-bromo groups would decelerate radical cyclization, because the HOMO-SOMO energy gap between their aromatic rings and the corresponding α-carbonyl radical intermediates would become larger. The reaction of α,β-unsaturated imides **1e** with *N*,*N*-dimethyl-3-methylaniline (**2g**) occurred in a regioselective manner at the *para*-position of the aromatic methyl group to give 1,2,3,4-THQ **5eg** exclusively because the aromatic methyl group served as the steric bulk in the radical cyclization step (Table 5(iii)). The reaction of *N*,*N*-dimethyl-3-fluoroaniline (**2h**) with α,β-unsaturated imide **1e** gave a mixture of 7-fluoro and 5-fluoro-1,2,3,4-THQs **5eh** in the ratio of 70:30. This result suggested that the fluoro group was sterically less demanding than the methyl group. Thus, radical cyclization would occur with low regioselectivity (See SI).

Table 5: Exploring of substrate scope.[a]



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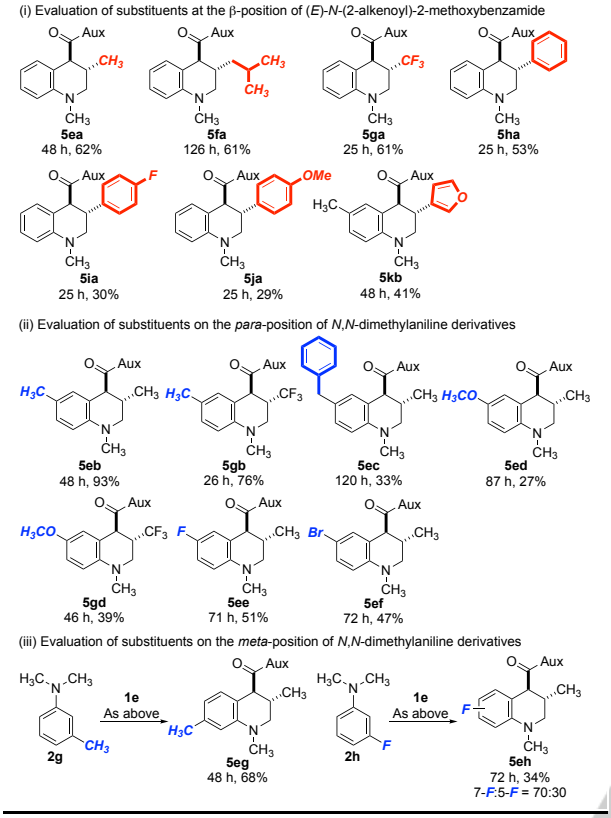
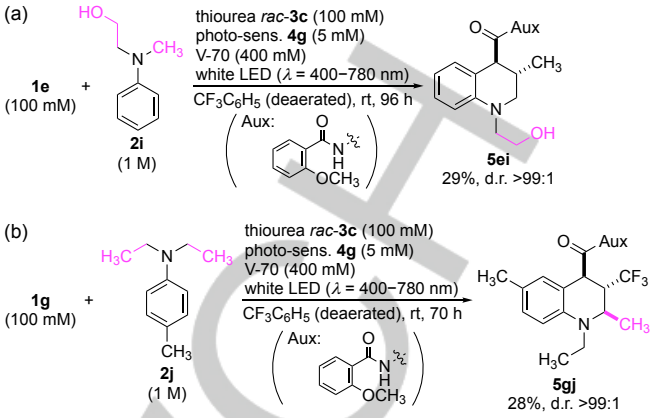


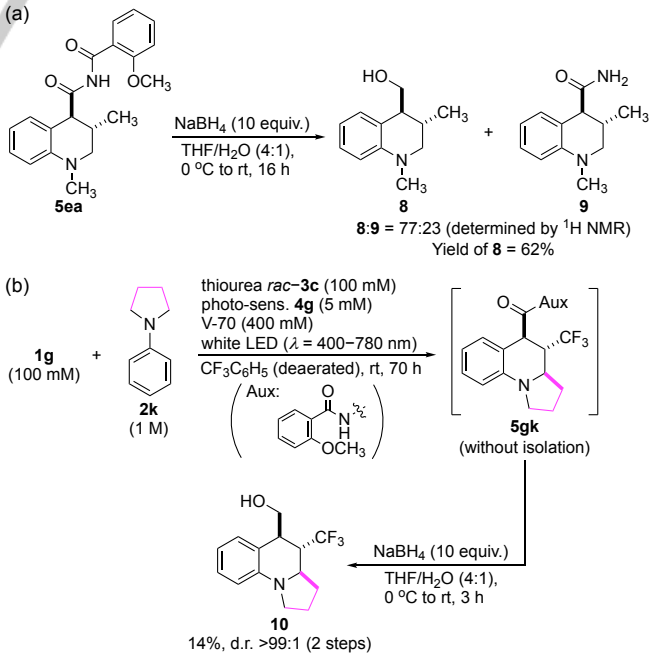
[a] All 1,2,3,4-THQs **5ea**-**5eg** were isolated with the exception of **5eh**.

We tried to carry out regioselective generation of α-aminoalkyl radicals and to introduce three contiguous stereogenic centers in 1,2,3,4-THQs (Scheme 2). The reaction of α,β-unsaturated imide **1e** with 2-(*N*-methylanilino)ethanol (**2i**) was investigated to achieve regioselective generation of an α-aminoalkyl radical followed by formation of 1,2,3,4-THQ **5ei** (Scheme 2a). A mechanism for regioselective formation of α-aminoalkyl radical would be explained by a stereoelectronic rule (see SI).[42] Next, we undertook the introduction of three contiguous stereogenic centers in a 1,2,3,4-THQ. We conducted the reaction of α,β-unsaturated imide **1g** with *N*,*N*-diethyl-4-methylaniline (**2j**) to give 1,2,3,4-THQ **5gj** with excellent diastereoselectivity (Scheme 2b). The relative configuration of 1,2,3,4-THQ **5gj** was determined by NMR, which proved to be 2,3-*trans*-3,4-*trans* (see SI).



Scheme 2. (a) Regioselective formation of α-aminoalkyl radical and 1,2,3,4-THQ forming reaction. (b) Construction of three contiguous stereogenic centers.

Cleavage of the carbon-nitrogen bond in the acyclic imide moiety of 1,2,3,4-THQ **5ea** was attempted (Scheme 3). The reaction was carried out by using $NaBH_4$ in THF/H_2O at room temperature to give alcohol **8** and carboxamide **9** in the ratio of 77:23 (Scheme 3a). Alcohol **8** was successfully isolated in 62% yield. Carboxamide **9** was obtained as a mixture of the 2-methoxybenzamide auxiliary. Accordingly, we synthesized **9** to identify the structure by using a different synthetic method (see SI). Formal [4+2] photo-cycloaddition of α,β-unsaturated imide **1g** with 1-phenylpyrrolidine **2k** was conducted to give a mixture of 1,2,3,4-THQ **5gk** and unknown by-products which was subsequently reacted with $NaBH_4$ to achieve the synthesis of a novel CF_3-containing benzo[*e*]indolizidine-5-methanol **10** (Scheme 3b).



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Scheme 3. (a) A chemoselective removal of the auxiliary. (b) A synthesis of a novel CF_3-containing benzo[*e*]indolizidine-5-methanol **10**.

To understand the initial process of the formal [4+2] photo-cycloaddition, we carried out quenching experiments of the Ir(III) complex **4g** fluorescence emission with acyclic α,β-unsaturated imide **1e**, *N*,*N*-dimethylaniline (**2a**), and thiourea *rac*–**3c** in CH_2Cl_2 (see SI). Among them, only *N*,*N*-dimethylaniline (**2a**) quenched Ir(III) complex **4g** emission. The Stern-Volmer constants ($k_q\tau$) and the quenching fraction of emission (η) were 2.19 x 10^5 M^{-1} and 99.9% for *N*,*N*-dimethylaniline (**2a**), respectively. Then, we determined the quantum yield by using $K_3[Fe(C_2O_4)_3]$ as a chemical actinometer.[43,44] As a result, the quantum yield ($\Phi_{\mathbf{5ga}}$) of the formation of 1,2,3,4-THQ **5ga** was determined to be 0.23 (see, SI). The quantum yield did not exceed 1.00, and therefore we could rule out the non-photochemical radical chain mechanism. The emission spectrum of the Ir(III) complex **4g** was successfully measured at 77 K in propionitrile/*n*-butyronitrile (4/5, v/v), which indicated that the maximum emission peak was observed at 2.67 eV (464 nm) as 0-0 transition frequency (see SI). We also carried out cyclic voltammetry (CV) analyses (see SI).

A plausible reaction mechanism is shown in Scheme 4. The reaction consists of two cycles, *i.e.*, an Ir complex photo-sensitizer mediated cycle and a thiourea-mediated cycle. Redox potentials mentioned as follows are the values obtained by CV analyses and calculated by Rehm-Weller equations (see SI).[44] In the Ir complex photo-sensitizer-mediated cycle, Ir(III) complex **4g** absorbs light to generate photo-excited state of Ir(III) complex **4g*** (*Ir(III)) which is a strong single electron oxidant ($E_{1/2}^{red}$ [*Ir(III)/Ir(II)] = +1.38 V versus Fc/Fc^+ in CH_3CN). The resulting photo-excited state of Ir(III) complex **4g*** (*Ir(III)) is subjected to reductive quenching by *N*,*N*-dialkylaniline **2** via SET to generate amine radical cation $\mathbf{2}^{\bullet+}$ (E_p^{ox} [$\mathbf{2}/\mathbf{2}^{\bullet+}$] = +0.41 V versus Fc/$Fc^+$ in CH_3CN) followed by PT, eventually producing α-aminoalkyl radical **A** and Ir(II) complex. The resulting Ir(II) complex ($E_{1/2}^{red}$ [Ir(III)/Ir(II)] = –1.29 V versus Fc/Fc^+ in CH_3CN) is oxidized by a large excess of V-70 to form anion radical of V-70 (V-$70^{\bullet-}$) ($E_{1/2}^{red}$ [V-70/V-$70^{\bullet-}$] = –1.29 V versus Fc/Fc^+ in CH_3CN) and converted to ground state Ir(III) complex **4g**. The radical anion of V-70 (V-$70^{\bullet-}$) is protonated to generate the hydrazyl radical. On the other hand, α,β-unsaturated imides **1** (E_n [$\mathbf{1e}/\mathbf{1e}^{\bullet-}$] = –1.31 V versus Fc/$Fc^+$ in CH_3CN) are not subject to the facile reduction caused by Ir(II) complex in the presence of excess amounts of V-70, which achieves not only increasing catalytic turnover of Ir(III) complex **4g**, but also prevents formation of the reduced product of α,β-unsaturated imide **1e**. In the thiourea-mediated cycle, thiourea *rac*-**3c** interacts with α,β-unsaturated imide **1e** to form hydrogen-bonded complex **B** in accordance with a reported model.[36] The resulting hydrogen-bonded complex **B** reacts with α-aminoalkyl radical **A** via RCA to form α-carbonyl radical intermediate **C**. The resulting intermediate **C** is subjected to cyclization to give cyclohexadiene π-radical intermediate **D** which subsequently undergoes SET followed by PT or HAT with V-70[25h,25j] to give 1,2,3,4-THQ **5** and the hydrazyl radical where HAS completes. The resulting hydrazyl radical generated from the two cycles would be converted to hydrazine via SET followed by PT or HAT by the reaction with cyclohexadiene π-radical intermediate **D** or Ir(II). We could not isolate the resulting hydrazine because of an unstable compound that leads to degradation products.[25e,25f,25g,25j]

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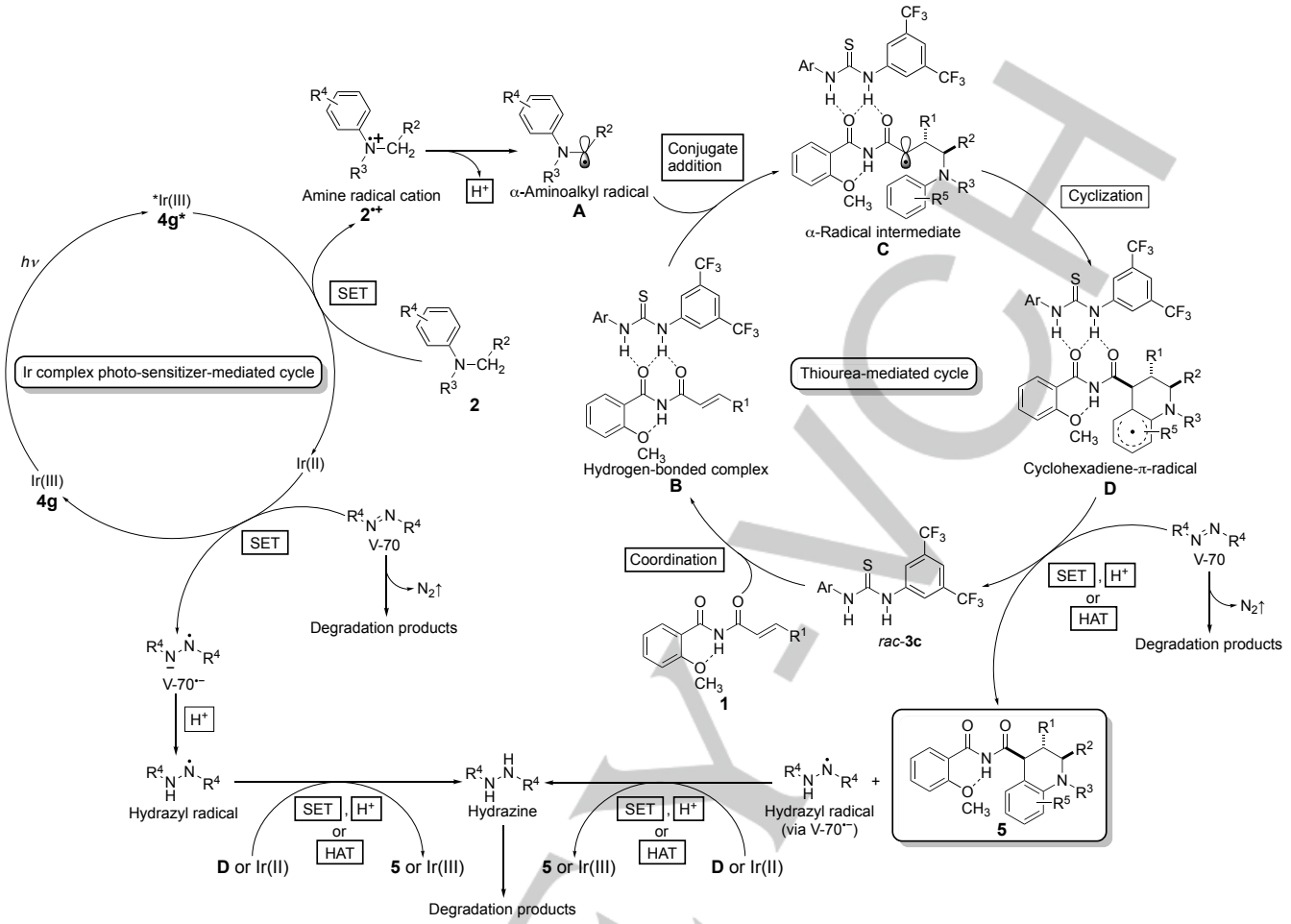

Scheme 4. Plausible reaction mechanism.

Conclusion

The cooperative action of a novel Ir(III) complex photo-sensitizer, a thiourea, and an azo compound have enabled the synthesis of structurally diverse 1,2,3,4-THQs possessing contiguous stereogenic centers in a highly diastereoselective manner (>99:1) via the visible-light-induced formal [4+2] cycloaddition of acyclic α,β-unsaturated amides and imides with *N*,*N*-dialkylanilines. The regioselective cyclization of α-carbonyl radical intermediates and the regioselective generation of α-aminoalkyl radicals from *N*,*N*-dialkylanilines have also been achieved. A chemoselective cleavage of the acyclic imide moiety of 1,2,3,4-THQs has been demonstrated. Further studies on development of a highly enantioselective reaction, elucidation of photophysical properties of a novel Ir(III) complex, and a biological assay of 1,2,3,4-THQs are under way.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Nitrogen heterocycles • Photo-reactions • Radical reactions • Conjugate addition • Aromatic substitution

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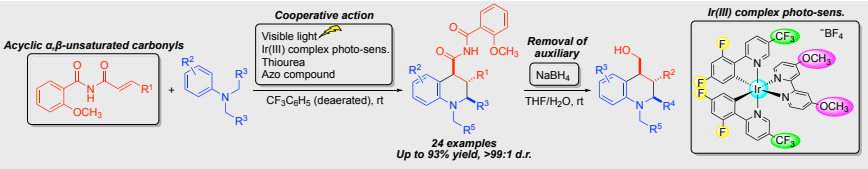

Kennosuke Itoh, Shun-ichi Nagao, Ken Tokunaga, Shigeto Hirayama, Fumika Karaki, Takaaki Mizuguchi, Kenichiro Nagai, Noriko Sato, Mitsuaki Suzuki, Masashi Hashimoto, Hideaki Fujii**

Page No. – Page No.

Formal [4+2] Reaction: The cooperative action of a novel Ir(III) complex photo-sensitizer, a thiourea, and an azo compound enables visible-light-induced formal [4+2] cycloaddition of acyclic α,β-unsaturated amides and imides with *N*,*N*-dialkylanilines to synthesize structurally diverse 1,2,3,4-tetrahydroquinolines possessing contiguous stereogenic centers in a highly diastereoselective manner (>99:1). A chemoselective removal of the auxiliary has been achieved.

Keywords: Nitrogen heterocycles • Photo-reactions • Radical reactions • Conjugate addition • Aromatic substitution