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Alkyl Radical Addition to Aliphatic and Aromatic *N*-Acylhydrazones Using an Organic Photoredox Catalyst

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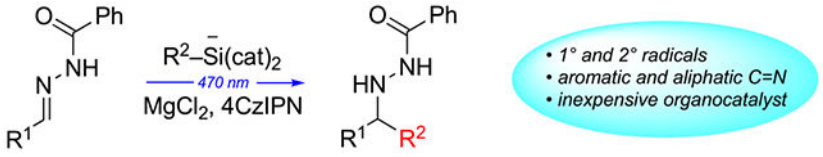
Abstract

Increased versatility of intermolecular radical addition to imino acceptors via photoredox catalysis is reported. Primary and secondary radicals, generated via visible-light photocatalysis from alkyl biscatecholatosilicates with organocatalyst 4CzIPN, add successfully to both aromatic and aliphatic *N*-acylhydrazones in the presence of $MgCl_2$. With *N*-benzoylhydrazones, a simple reductive cleavage of the N-N bond of the hydrazine adduct furnishes the free amine. Synthetic utility is exemplified in a synthetic application toward repaglinide, a clinically important hypoglycemic agent.

Graphical Abstract



A mines are prevalent in natural products, drugs, and other biologically significant molecules, underlining the importance of developing efficient methods for their synthesis.[1] Expanding upon classical imine reduction and addition methods,[2] recent developments in this area include transition-metal-catalyzed hydroamination of alkenes and other C-N bond constructions.[3] However, imines remain attractive amine precursors because of their ready availability from a wide range of commercial materials and also the versatility for either C-C or C-H bond constructions at the imine carbon to form chiral α-branched amines.[1] Often, such reactions have limited applicability to imines from aliphatic aldehydes, as these substrates are subject to competing aza-enolization by deprotonation of the α-carbon.[4] We have addressed this issue through the use of radical additions to C=N bonds of hydrazones.[5–7] In support of that objective, our group developed a versatile Mn-mediated radical addition to chiral *N*-acylhydrazones, which enabled the asymmetric synthesis of chiral amines using both primary and secondary radicals (Scheme 1a).[8] These reactions are compatible with additional functionality in both radicals and acceptors, facilitating

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03053.

Experimental procedures, spectral data for new compounds, and determination of percent conversion for Table 1 (PDF)

The authors declare no competing financial interest.

applications in complex molecule synthesis.[9,10] While very effective for aliphatic imino acceptors, the Mn-mediated additions were unsuccessful with hydrazones derived from aromatic aldehydes. Conversely, Molander recently reported radical additions to *N*-sulfonylimines and *N*-phenylimines that are effective for aromatic acceptors, but incompatible with imines from aliphatic aldehydes.[11] These reactions use organosilicate salts as radical precursors in the presence of the organic photoredox catalyst 4CzIPN (Scheme 1b).[12] Informed by our prior successes with radical additions to aliphatic *N*-acylhydrazones, we hypothesized that a combination of *N*-acylhydrazone radical acceptors with photoredox-catalyzed radical generation would lead to improved versatility in radical additions to C=N bonds. Here, we report a carbon–carbon bond constructive amine synthesis method that (a) takes advantage of the excellent radical acceptor behavior of the *N*-acylhydrazone functional group, (b) adopts catalytic conditions for radical generation, and (c) expands the versatility of photoredox-catalyzed radical additions to include both aliphatic and aromatic imino acceptors (Scheme 1c).

Recent developments in photoredox catalysis have impacted a wide variety of radical transformations,[13] including radical additions to imino acceptors.[14] We planned to exploit *N*-acylhydrazones such as **1a** (Table 1) as radical acceptors, using the known reductive quenching of photoexcited 4CzIPN by alkyl bis-catecholatosilicates to generate alkyl radicals. We envisioned that the proven Lewis acid promoted radical acceptor properties of *N*-acylhydrazones could expand the versatility of such reactions; hydrazones have not yet been exploited in reductive additions to C=N bonds via photoredox catalysis.[11b] After radical addition, SET reduction and proton transfer to the intermediate aminyl radical would furnish the desired adduct and also regenerate 4CzIPN.

Toward this end, our initial experiments sought to test whether this photoredox catalysis cycle could be completed with C=N acceptors lacking an anion-stabilizing *N*-substituent such as sulfonyl; the efficiency of aminyl radical reduction and catalyst turnover was in question. Indeed, *N*-acylhydrazones are compatible with this redox cycle: In an initial trial at 15 mol % loading of photocatalyst 4CzIPN, cyclohexyl silicate addition to **1a** proceeded in DMSO solution with 40% conversion to **2a** over 24 h (Table 1, entry 1). Although this result demonstrated successful photocatalyst turnover, the modest conversion did not increase via longer reaction time (entry 2). Next, a variety of Lewis acids (2 equiv) were tested in order to assess the potential for enhanced reactivity via chelation of the *N*-acylhydrazone[8,10a] (entries 3–10), with $ZnBr_2$ and $MgCl_2$ offering the most improved results (see the Supporting Information for results with various Lewis acids). Increased Lewis acid loading did not improve reactivity (compare Table 1, entries 5 and 7).

Aside from DMSO, other solvents were screened and found to be inferior; we attribute this to alkyl silicate insolubility problems (entries 11–13). Reaction time, catalyst loading, and silicate stoichiometry were also examined and gratifyingly led to greatly improved conversion (entry 17); these conditions were selected as a starting point to test substrate scope (entry 17).

As noted above, one of our main goals for this project was a versatile method tolerant of both aliphatic and aromatic substituents at the C=N bond. Complementing the result with

benzaldehyde *N*-acylhydrazone **1a** (Table 2, entry 1), cyclohexyl addition to aliphatic *N*-acylhydrazones **1b** and **1c** occurred in modest isolated yields in the presence of unbranched alkyl groups (entries 2 and 3); branching at the α-position of the hydrazone was detrimental to yield (entries 4 and 5). Additions of more reactive primary radicals furnished expected adducts in low yield (entries 6–8), presumably impacted by premature quenching through H-abstraction.

While Table 2 demonstrated some potential for improved versatility, yields were not consistently at a practical level. Fortunately, further scope studies revealed that *N*-benzoylhydrazones were superior to the hydrazones of Tables 1 and 2. Cyclohexyl addition to *N*-benzoylhydrazones **6a**–**6c** gave significant improvement to 79–94% isolated yield (Table 3, entries 1–3). When silicate loading was reduced from 3 to 1.5 equiv and catalyst loading was lowered from 15 to 5 mol %, the yield of **7a** was only slightly diminished from 79% to 75% (entry 1). Additions to aliphatic *N*-benzoylhydrazones **6d** and **6e** also afforded improved yield versus their analogues in Table 2. Importantly, a 15-fold scaleup to 1 g of **6d** afforded 60% yield of **7d** (entry 4). Cyclohexyl additions to a series of substituted benzaldehyde hydrazones showed tolerance for the presence of electron-donating or -withdrawing effects, and identical yields were obtained when ortho versus para substituents were compared (entries 2, 3, 6, and 7). As before, the effect of branching on the α-carbon for *N*-benzoylhydrazones was detrimental to radical addition (entry 5).

The diversity of alkyl radicals suitable for this transformation was next examined (Scheme 2). Primary alkyl silicates were added to *N*-benzoylhydrazones using the conditions described previously (Table 3) to afford adducts **8**–**13**. Tolerance of heteroatoms either on the alkyl radical (**10** and **11**) or on the hydrazone acceptor (**7c**, **7g**, **7h**, **12**, and **13**) suggests that various functional group manipulations (including transitionmetal-catalyzed cross coupling) can be sequenced with these radical additions.

Previously, we have observed that hydrazines bearing *N*-benzoyl functionality readily undergo N-N bond reduction with SmI_2 to liberate the free amine.[15] Treatment of adduct **7a** with SmI_2 yielded free amine **14** in 66% yield (Scheme 3). In combination with the functional group compatibilities of the radical addition, the ease of N-N bond cleavage enhances the potential for applications in syntheses of more complex targets.

As a demonstration of synthetic utility, we targeted repaglinide, a drug that stimulates insulin production to combat diabetic hyperglycemia.[16] Nucleophilic aromatic substitution of commercially available 2-fluorobenzaldehyde with piperidine, followed by condensation with benzoic hydrazide ($BzNHNH_2$), afforded hydrazone **16** in excellent yield. Photoredox-catalyzed isobutyl addition then provided **17**, the chiral amine portion of repaglinide (Scheme 4). It is noteworthy that the bulky o-piperidinyl substituent is tolerated in this radical addition.

Amine synthesis has always been a critical undertaking in organic chemistry, given that amines are commonly found in a broad spectrum of compounds of biological importance. The *N*-acylhydrazone radical acceptors herein allow both aromatic and aliphatic aldehydes to undergo carbon–carbon bond constructive synthesis of amines, facilitating access to a

broad range of valuable building blocks for drug discovery. Considering the asymmetric induction strategies we have previously developed for hydrazone radical acceptors,[17] further advances in this direction may be anticipated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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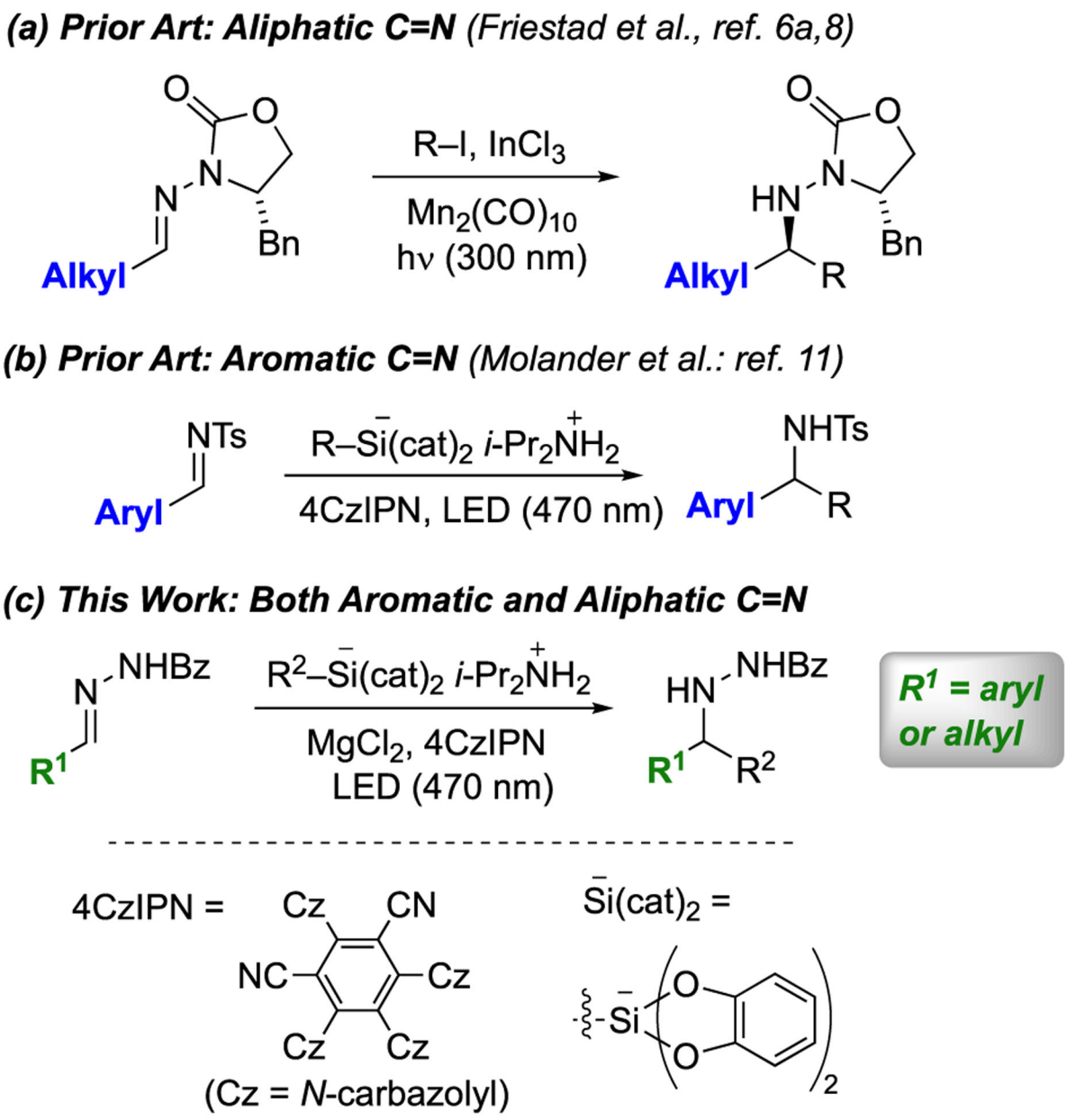
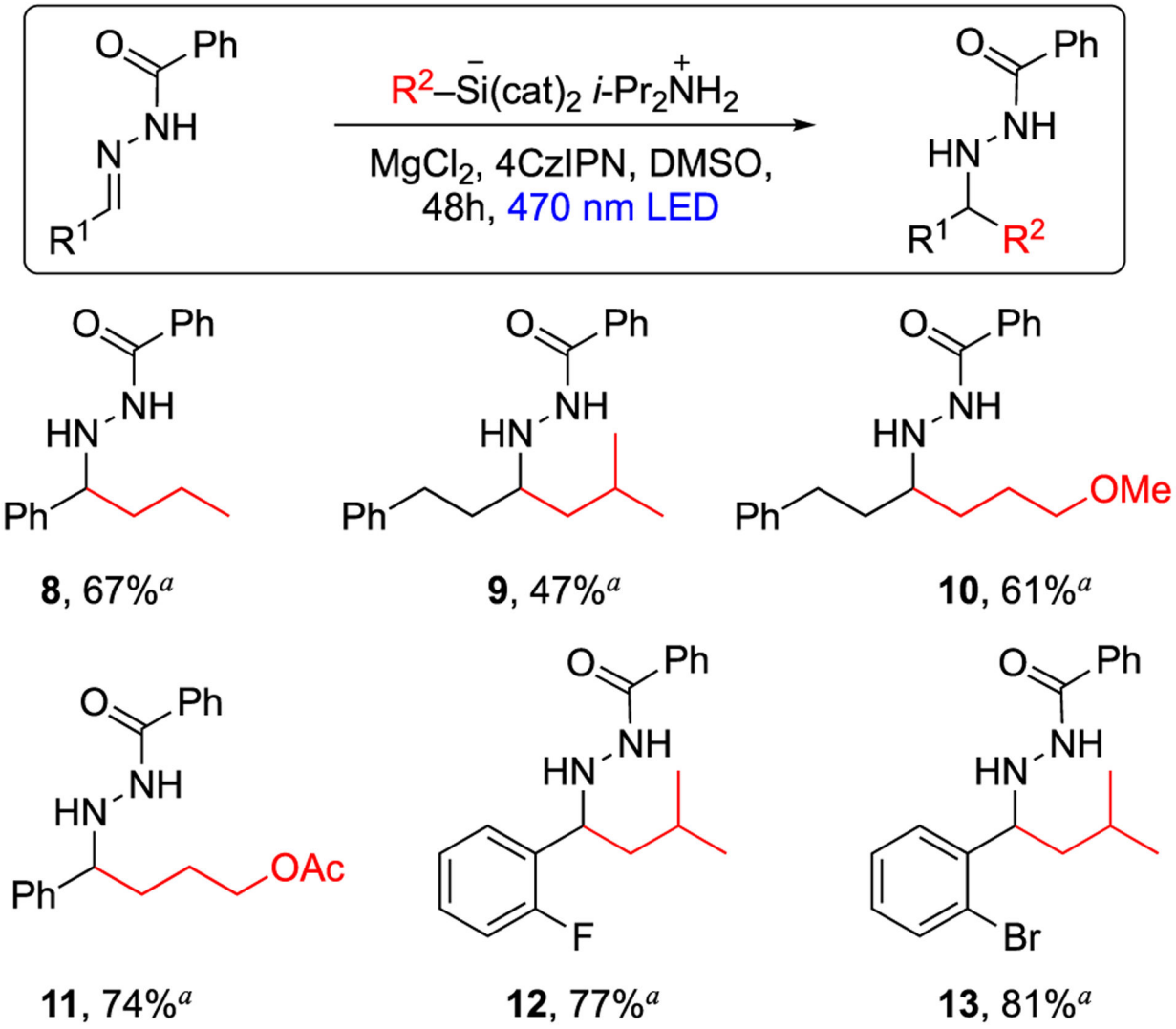


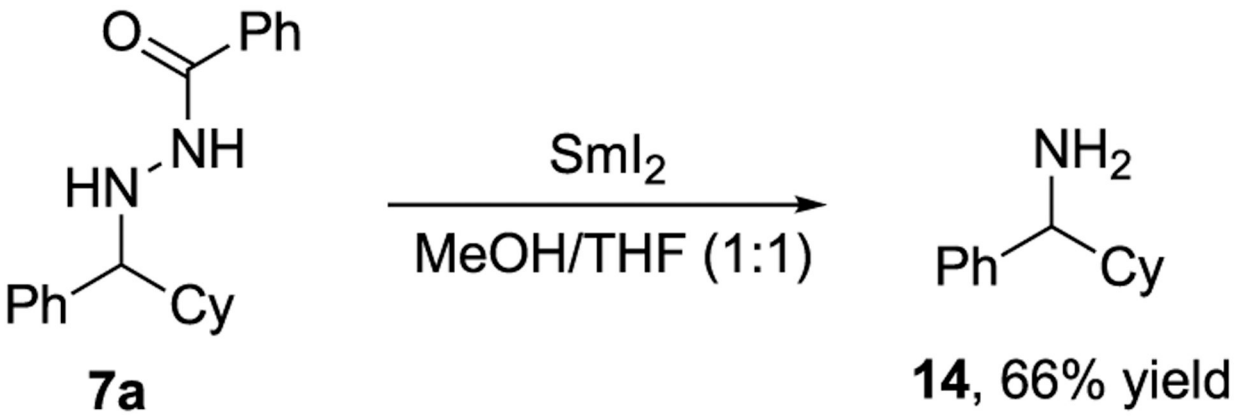
Scheme 1.
Bridging a Gap in Radical Addition to C=N



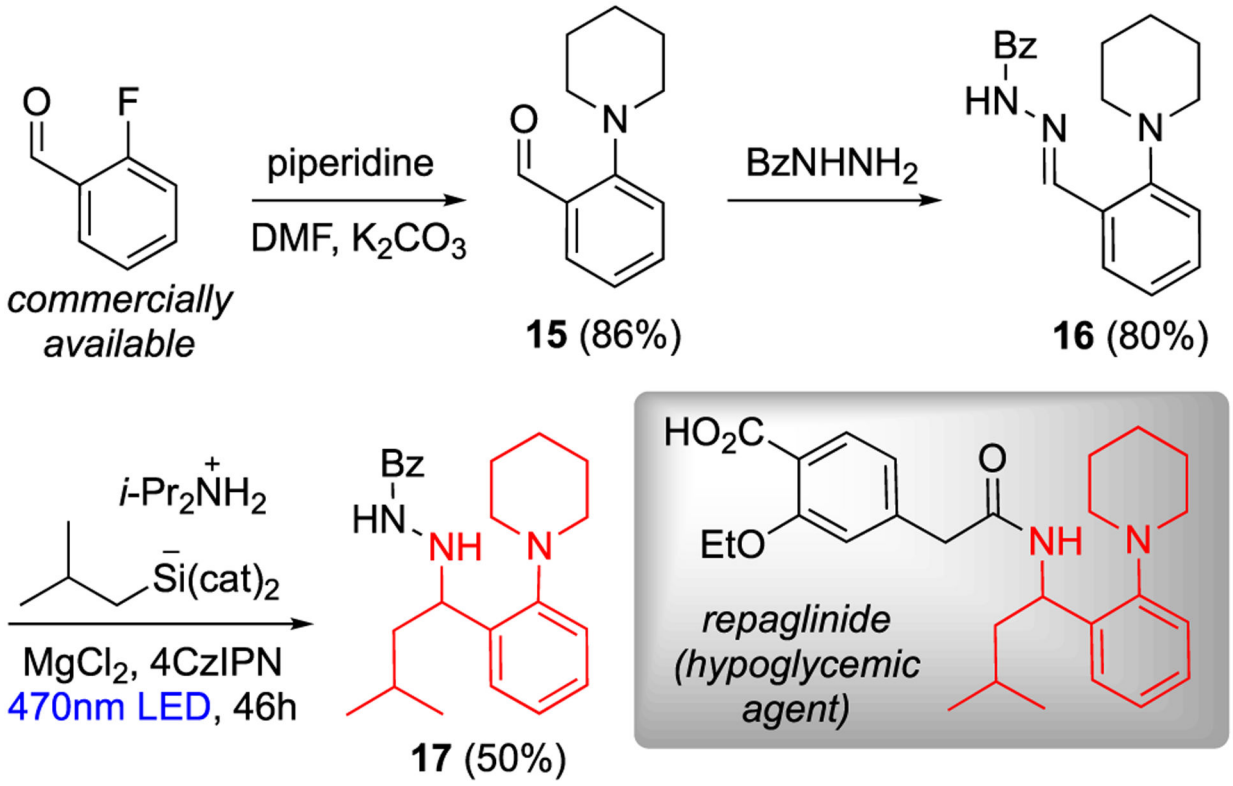
Scheme 2.

Addition of 1° Radicals to *N*-Benzoylhydrazones

[a]1.5 eq silicate and 5 mol % 4CzIPN used. [b]Three eq silicate and 15 mol % 4CzIPN used



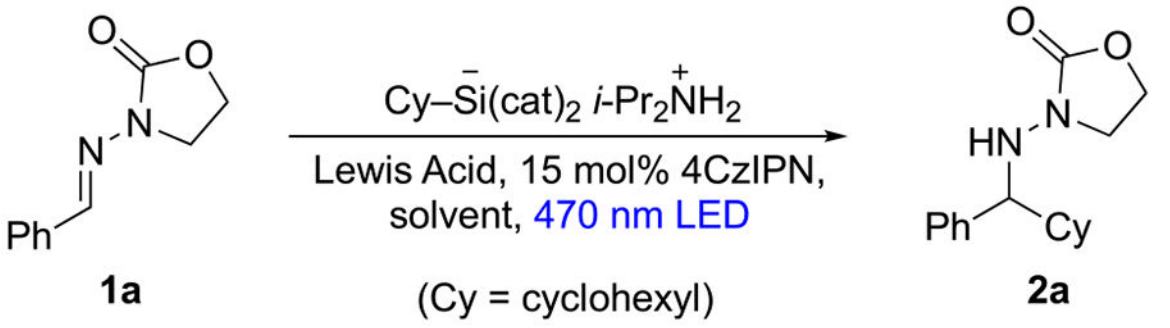
Scheme 3.
Accessing a Primary Amine by N-N Cleavage



Scheme 4.
Progress toward Formal Synthesis of Racemic Repaglinide

Table 1.

Optimization of Radical Addition Reaction



entry	Lewis acid (2 equiv)	silicate (equiv)	solvent	time (h)	% conv[a]
1	none	2	DMSO	24	40
2	none	2	DMSO	49	48
3	$ZnBr_2$	1	DMSO	18	27
4	$Zn(OTf)_2$	1	DMSO	18	27
5	$ZnBr_2$	2	DMSO	18	63
6	$ZnBr_2$	4	DMSO	18	64
7	$ZnBr_2$ (3 equiv)	2	DMSO	18	49
8	$MgCl_2$	2	DMSO	18	59
9	$MgBr_2$	2	DMSO	18	54
10	$Mg(OTf)_2$	2	DMSO	18	31
11	$ZnBr_2$	2	DMF	16	28
12	$MgCl_2$	2	DMF	16	44
13	$MgCl_2$	1.2	EtOH	23	10
14	$MgCl_2$	2.6	DMSO	48	86
15	$MgCl_2$	3	DMSO	48	22[b]
16	$MgCl_2$	3	DMSO	48	68[c]
17[d]	$MgCl_2$	3	DMSO	47	88 (60[e])
18	$MgCl_2$	2	DMSO	24	73

[a] Determined by ^1H NMR integration.

[b] 1 mol % of catalyst loading.

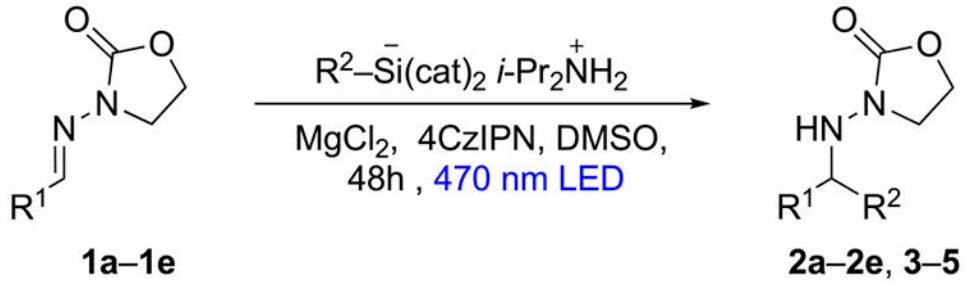
[c] 5 mol % of catalyst loading.

[d] Conversions in control experiments using conditions of entry 17: Absence of blue LED (0%), absence of 4CzIPN (0%), open to air (67%), replacing silicate with $CyBF_3K$ (59%).

[e] Isolated yield.

Table 2.

N-Acylhydrazone Compatibility Study with Secondary and Primary Radical Addition

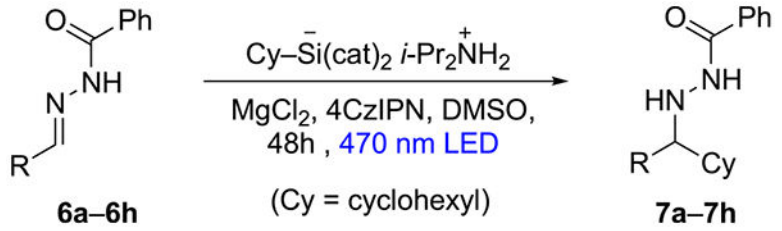


entry	R^1	product	R^2	yield[a] (96)
1	Ph **(la)**	**2a**	Cy	60
2	$PhCH_2CH_2$ **(lb)**	**2b**	Cy	28
3	*n*-C_5H_{11} **(lc)**	**2c**	Cy	22
4	*i*-Pr **(Id)**	**2d**	Cy	19
5	*t*-Bu **(le)**	**2e**	Cy	0
6	Ph **(la)**	**3**	*n*-Pr	45
7	Ph **(la)**	**4**	$PhCH_2CH_2$	21
8	PhCH,CH, **(lb)**	**S**	*i*-Bu	14

[a]Used 3 equiv of silicate and 15 mol % of 4CzIPN.

Table 3.

Addition of Alkyl Radicals to Aliphatic and Aromatic *N*-Benzoylhydrazones, Including Gram-Scale Reaction



6a–6h **7a–7h**

entry	R	product	yield (%)
1	Ph **(6a)**	7a	79[a] (75[b])
2	*p*-tolyl **(6b)**	7b	94[a]
3	*p*-ClC_6H_4 **(6c)**	7c	84[a]
4	$PhCH_2CH_2$ **(6d)**	7d	63[b](60[c])
5	*i*-Pr **(6e)**	7c	25[b]
6	*o*-tolyl **(6f)**	7f	94[a]
7	*o*-$C1C_6H_4$ **(6g)**	7g	84[a]
8	4-$(Me_2N)C(sH_4$ **(6h)**	7h	32[a]

[a]0.1–0.3 mmol of **6**, 3 equiv of silicate, and 15 mol % of 4CzIPN.

[b]1.5 equiv of silicate and 5 mol % of 4CzIPN.

[c]Gram-scale reaction (4 mmol).