Published in final edited form as:
Org Lett. 2022 June 17; 24(23): 4176–4181. doi:10.1021/acs.orglett.2c01409.

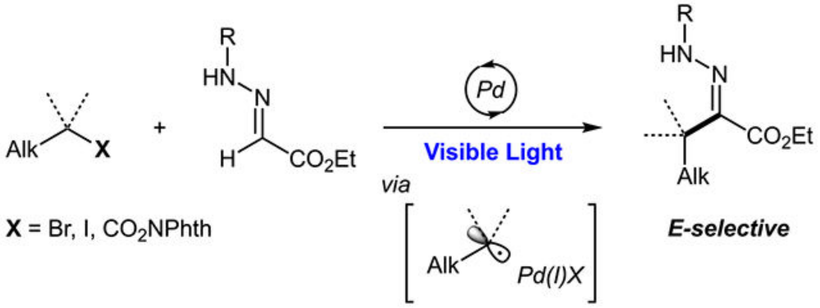
Accessing Illusive *E* Isomers of *α*-Ester Hydrazones via Visible-Light-Induced Pd-Catalyzed Heck-Type Alkylation

Nikita Kvasovs,
Vladimir Gevorgyan
Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States

Abstract

A visible-light-induced Pd-catalyzed stereoselective synthesis of alkylated ester hydrazones has been developed. This method operates via generation of a nucleophilic carbon-centered radical from alkyl bromide, iodide, or redox-active ester, followed by its addition to hydrazone, and a subsequent desaturation by palladium. The majority of products have *E* configuration, which are inaccessible by conventional condensation methods. In addition, a sequential C,N-alkylation protocol has been developed: a reaction between 1,3-dihalides and glyoxylate-derived hydrazone, delivering tetrahydropyridazines.

Graphical Abstract



Hydrazone is a highly versatile functional group within the organic chemistry domain. It is most famous for use as a precursor/intermediate in synthesis of various electron-rich heterocycles, such as pyrazoles[1] and indoles,[2] as well as in azaenolate reactions[3] and carbene chemistry.[4] Beyond synthetic chemistry, hydrazones are used in bioconjugation,[5] polymer,[6] and material[7] chemistry. A number of hydrazone-containing molecules exhibit biological activity, which paves the way for drug discovery.[8] Classically, hydrazones are accessed via condensation reactions of carbonyls with hydrazines.[9] Quite simple,

---

Corresponding Author Vladimir Gevorgyan – Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States, vlad@utdallas.edu.

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c01409.
Experimental procedures and analytical data for all new compounds (PDF)

The authors declare no competing financial interest.

this method is reliant on availability of corresponding aldehyde or ketone and may not be a facile route for diversification. Moreover, sometimes forcing conditions (heat and acid) are required to achieve the desired transformation, which may become troublesome in the presence of certain sensitive functional groups. A direct C—H functionalization of aldehyde-derived hydrazones appears as an attractive alternative for rapid assembly of fully substituted hydrazones, which could bypass these challenges. Primarily, such functionalization can be achieved via radical chemistry of hydrazones. Hydrazones have long been recognized as good nucleophilic radical acceptors.[10] On the basis of this property, a number of reductive C—C bond-forming reactions have emerged (Scheme 1a),[10,11] including asymmetric reactions,[12] ultimately leading to chiral amines. The oxidative version of this transformation was recently realized in the form of perfluorinated radical addition (Scheme 1b).[13] Use of a copper or photoredox catalyst or stoichiometric oxidant ensures regeneration of the carbon—nitrogen double bond to restore valuable hydrazone functionality. Alternatively, the C═N double bond could be preserved via the radical addition/elimination strategy used in closely related oxime-type substrates;[14] however, this route has not been realized for hydrazones. As a result, at this point, there are only few non-fluorinated radical examples present in the literature,[15] which means that, even though oxidative C—H alkylation is possible, it remains quite limited in the choice of radical precursors to date. In addition, these reactions most often rely on use of dialkyl-substituted hydrazones, which may prevent further functionalization, such as employment in indole synthesis.[13] A non-radical C—H alkylation/arylation pathway is also possible, usually via pseudo-enolate-type reactions, but these examples are scarce and limited to very specific systems.[16] On the basis of the broad application of hydrazones within synthetic chemistry[1-4] and beyond,[5-8] development of a more general C—H alkylation protocol is warranted. Herein, we report a mild visible-light-induced stereoselective Pd-catalyzed Heck-type C—H alkylation of glyoxylate-derived hydrazones proceeding via nucleophilic radical addition (Scheme 1c).[17] The reaction exhibits a remarkable stereoselectivity, yielding a significantly less thermodynamically stable *E* isomer, allowing for the exploration of previously inaccessible chemical space.

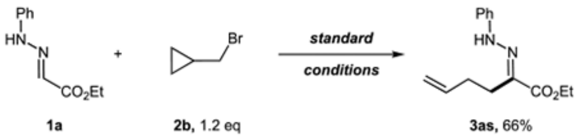
In last few years, the visible-light-induced photoexcited chemistry of palladium has emerged as a powerful tool for combining carbon-centered radical chemistry with innate properties of palladium complexes.[18] As a part of the field, previously hard-to-realize intermolecular alkyl-Heck-type[19] transformations of styrenes and other activated alkenes[20] and oximes[21] have been developed using an array of alkyl radical precursors. Motivated by these findings, we were eager to explore potential application of this approach to achieve a critical C—H alkylation of hydrazones.

A set of conditions was identified for coupling hydrazone **1** with cyclohexyl bromide **2** (see the Supporting Information for details). Suprisingly, the obtained product had an *E* configuration, despite the fact that the *Z* isomer is significantly more thermodynamically stable as a result of internal hydrogen bonding.[22] Importantly, in a typical condensation reaction, the *Z* isomer is either a sole or a predominant product in most cases.[23] While it is possible to synthesize the *E* isomer via other routes, typically, these involve reactions between organolithium reagents and diazo compounds[24] or silyl-enol ethers with diazonium salts[25] and, thus, have very low functional group tolerance. This means that our method not only allows for an unprecedented radical C—H alkylation of hydrazones but also allows for the synthesis of stereoisomers, which are not available otherwise.

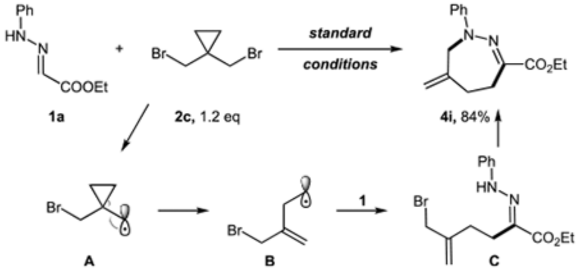
With the optimized conditions in hand, we began investigation of the reaction scope by interrogating reactions of various primary alkyl electrophiles with benchmark hydrazone **1** (Scheme 2). Alkyl bromide (**3a**), iodide (**3n**), and redox-active ester (**3p**) all have been found to be suitable radical precursors. Functional groups, such as phenyl (**3b**), terminal alkene (**3c**), ester (**3d**), ether (**3e**), and nitrile (**3f**), were all tolerated under these reaction conditions. The synthesis of bromoethanol derivative **3g**, however, required a protecting group. The slightly more electrophilic trimethylsilyl-methylene radical has also engaged in the reaction with hydrazone, although delivering a product with a slightly diminished yield (**3o**). Perhaps the most surprising results in the investigation of primary electrophiles were reactions of benzylic bromides (**3h–3m**). Engagement of benzylic electrophiles in alkyl-Heck reactions via hybrid Pd radical chemistry remains a challenge. Excitingly, under a slightly modified procedure,[26] we were able to achieve the desired transformation with moderate efficiency. Even more surprising was the fact that, out of all tested substrates, *ortho*-bromobenzyl bromide has proven to be the best reactant, with bromide functionality remaining untouched (**3m**). Moreover, secondary alkyl substrates, including acyclic (**3r**) or cyclic compounds with various ring sizes (**3s–3v**), could all be used via this protocol. A direct comparison between cyclohexyl bromide, iodide, and redox-active ester (**3v**) led to the conclusion that alkyl bromides are the most effective substrates in general. Hydrazones possessing various six-membered saturated heterocycles (**3w–3y** and **3ab**) could also be accessed. Furthermore, this transformation can be incorporated in a cascade reaction, where the first radical 1,5-*exo*-trig cyclization is followed by the addition to hydrazone, resulting in a bicyclic product (**3z**). Excitingly, reactions leading to compounds **3x** and **3z** proceeded with high degrees of diastereocontrol. Tertiary substrates, as opposed to primary and secondary substrates, with few exceptions (**3af** and **3aj**), resulted in products with a *Z* configuration. An increased steric repulsion as a result of a 1,3-allylic strain exhibited in a potential *E* isomer could be the reason for the reversed stereochemistry in these cases. Intriguingly, initial isolation of adamantyl-containing product **3ad** revealed the presence of the corresponding diazene **3ad'**. Diazene isomerized into the product overnight in slightly acidic non-neutralized $CDCl_3$.[26] Next, the scope of hydrazones was studied with emphasis placed on *N*-aryl hydrazones, en route to substituted indoles. In general, different functional groups on the aromatic ring did not influence the reaction outcome greatly, except for the *para*-nitrile substituent, where a *Z* stereoisomer **3am** was obtained. It could be explained by an increased acidity of the NH proton, making this hydrazine susceptible to base-induced isomerization. Excitingly, alkyl-substituted hydrazone **3aq** could also be obtained in a moderate yield via this protocol. Surprisingly, when benzyl-substituted hydrazone was employed, a regioisomeric non-ester-conjugated hydrazone product **3ar** was obtained.

Importantly, because these reaction conditions lead to *E* products, the nitrogen atom is preset for a potential intramolecular S_N2 reaction if an appropriate electrophile is present.[27] Indeed, employment of simple 1,3-dibromopropane under standard reaction conditions with an addition of another equivalent of a base led to 1,4,5,6-tetrahydropyridazine (**4a**) in a good yield (Scheme 3). Via this manner, several six-membered heterocycles were synthesized, including the phenyl-substituted product (**4c**), (*S*)-epiclorohydrin derivative (**4e**), 4,6- and 5,6-spirocycles (**4f** and **4g**), and difluoro-containing product (**4h**).

The formation of the carbon-centered radical was validated by reactions of (bromomethyl)cyclopropane under standard reaction conditions, which led to a ring-opening product **3as** in a moderate yield (eq 1). Notably, when bis(bromomethyl)cyclopropane **2c** was employed, a seven-membered heterocycle containing an endocyclic alkene **4i** was obtained (eq 2).



(1)



(2)

On the basis of the relevance of the reported light-induced Heck reactions of olefins[18,20a] and C—H alkylation of oximes,[21] together with the above-mentioned observations, the following mechanism is proposed (Scheme 4). Initially, visible-light-induced alkyl Pd hybrid species **A** is produced, followed by the favorable[10] radical addition to the C═N bond of hydrazone. The formed intermediate **B** could be either directly oxidized into diazene **D** or recombined with Pd(I) to form Pd(II) complex **C**, which, in turn, would undergo a *β*-hydride-type elimination to deliver diazene **D**. Diazene intermediacy is supported by its observation in the synthesis of adamantyl derivative **3ad** (*vide supra*) as well as obtaining the non-ester conjugated regioisomer **3ar**. The formation of the latter presumes intermediacy of the proposed diazene intermediate, which forms upon selective isomerization, driven by conjugation with the aromatic ring, as opposed to that with the ester group. It must be noted, however, that, in cases of primary and secondary alkyl radicals, the diazene intermediate was not detected during the reaction progress. This may imply that base-assisted isomerization of diazenes into products is very facile. *E* selectivity of obtained products could be explained by palladium-assisted isomerization, where Pd is chelated by oxygen and nitrogen atoms, thus pushing the other nitrogen away from the ester group. Alternatively, *E* hydrazone may arise from fast kinetically favorable isomerization of diazene, which appears irreversible under basic conditions. Otherwise, even in slightly acidic $CDCl_3$, a rapid complete isomerization of *E* products to *Z* products occurs at room temperature.[26]

In conclusion, we developed a mild visible-light-induced Pd-catalyzed Heck-type alkylation of glyoxylate-derived hydrazones proceeding via a hybrid Pd radical mechanism. The major highlight of the presented work is an excellent stereoselectivity, enabling synthesis of previously hard-to-access *E* isomers of ester-containing hydrazones. Unique stereoselectivity of the process was also used in a sequential C,N-alkylation reaction toward one-pot construction of tetrahydropyridazines. We hope that this work will spark further interest in development of new C—H functionalization of imine-type compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the National Institute of Health (GM120281), the National Science Foundation (CHE-1955663), and the Welch Foundation (Chair, AT-0041) for financial support.

REFERENCES

(1). Karrouchi K; Radi S; Ramli Y; Taoufik J; Mabkhot YN; Al-aizari FA; Ansar M. h. Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review. Molecules 2018, 23, 134. [PubMed: 29329257]

(2) (a). Robinson B The Fischer Indole Synthesis. Chem. Rev 1963, 63, 373–401.(b)Humphrey GR; Kuethe JT Practical Methodologies for the Synthesis of Indoles. Chem. Rev 2006, 106, 2875–2911. [PubMed: 16836303] (c)Taber DF; Tirunahari PK Indole Synthesis: A Review and Proposed Classification. Tetrahedron 2011, 67, 7195–7210. [PubMed: 25484459]

(3) (a). Lazny R; Nodzewska A *N,N*-Dialkylhydrazones in Organic Synthesis. From Simple *N,N*-Dimethylhydrazones to Supported Chiral Auxiliaries. Chem. Rev 2010, 110, 1386–1434. [PubMed: 20000672] (b)de Gracia Retamosa M; Matador E; Monge D; Lassaletta JM; Fernández R Hydrazones as Singular Reagents in Asymmetric Organocatalysis. Chem.—Eur. J 2016, 22, 13430–13445. [PubMed: 27552942]

(4) (a). Barluenga J; Moriel P; Valdés C; Aznar F N-Tosylhydrazones as Reagents for Cross-Coupling Reactions: A Route to Polysubstituted Olefins. Angew. Chem., Int. Ed 2007, 46, 5587–5590. (b)Radolko J; Ehlers P; Langer P Recent Advances in Transition-Metal-Catalyzed Reactions of N-Tosylhydrazones. Adv. Synth. Catal 2021, 363, 3616–3654.

(5). Kölmel DK; Kool ET Oximes and Hydrazones in Bioconjugation: Mechanism and Catalysis. Chem. Rev 2017, 117, 10358–10376. [PubMed: 28640998]

(6). García F; Smulders MMJ Dynamic Covalent Polymers. J. Polym. Sci., Part A: Polym. Chem 2016, 54, 3551–3577.

(7) (a). Shao B; Aprahamian I Hydrazones as New Molecular Tools. Chem 2020, 6, 2162–2173. (b)Tatum LA; Su X; Aprahamian I Simple Hydrazone Building Blocks for Complicated Functional Materials. Acc. Chem. Res 2014, 47, 2141–2149. [PubMed: 24766362]

(8) (a). de Oliveira Carneiro Brum J; França CCT; LaPlante RS; Villar DFJ Synthesis and Biological Activity of Hydrazones and Derivatives: A Review. Mini-Rev. Med. Chem 2020, 20, 342–368. [PubMed: 31612828] (b)Rollas S; Küçükgüzel SG Biological Activities of Hydrazone Derivatives. Molecules 2007, 12, 1910–1939. [PubMed: 17960096] (c)Verma G; Marella A; Shaquiquzzaman M; Akhtar M; Ali M; Alam M A Review Exploring Biological Activities of Hydrazones. J. Pharm. Bioallied Sci 2014, 6, 69–80. [PubMed: 24741273]

(9). Sayer JM; Pinsky B; Schonbrunn A; Washtien W Mechanism of Carbinolamine Formation. J. Am. Chem. Soc 1974, 96, 7998–8009.

(10). Friestad GK Addition of Carbon-Centered Radicals to Imines and Related Compounds. Tetrahedron 2001, 57, 5461–5496.

(11) (a). Cullen STJ; Friestad GK Alkyl Radical Addition to Aliphatic and Aromatic N-Acylhydrazones Using an Organic Photo-redox Catalyst. Org. Lett 2019, 21, 8290–8294. [PubMed: 31560554] (b)Friestad GK; Ji A Mn-Mediated Coupling of Alkyl Iodides and Ketimines: A Radical Addition Route to α,α-Disubstituted α-Aminoesters. Org. Lett 2008, 10, 2311–2313. [PubMed: 18461956]

(12) (a). Rono LJ; Yayla HG; Wang DY; Armstrong MF; Knowles RR Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization. J. Am. Chem. Soc 2013, 135, 17735–17738. [PubMed: 24215561] (b)Friestad GK Radical Additions to Chiral Hydrazones: Stereoselectivity and Functional Group Compatibility. In Radicals in Synthesis III; Heinrich M, Gansäuer A, Eds.; Springer: Berlin, Germany, 2012; Topics in Current Chemistry, Vol. 320, pp 61–91, DOI: 10.1007/128_2011_163.

(13). Xu X; Zhang J; Xia H; Wu J C(sp^2)—H Functionalization of Aldehyde-Derived Hydrazones Via a Radical Process. Org. Biomol Chem 2018, 16, 1227–1241. [PubMed: 29431815]

(14) (a). Clive DLJ; Subedi R Radical Cyclization of O-Trityl Oximino Esters: A Ring Closure That Preserves the Oxime Function. Chem. Commun 2000, 237–238.(b)Kim S; Lee IY; Yoon J-Y; Oh DH Novel Radical Reaction of Phenylsulfonyl Oxime Ethers. A Free Radical Acylation Approach. J. Am. Chem. Soc 1996, 118, 5138–5139.(c)Kim S; Yoon J-Y Free Radical-Mediated Ketone Synthesis from Alkyl Iodides Via Sequential Radical Acylation Approach. J. Am. Chem. Soc 1997, 119, 5982–5983.

(15) (a). Prieto A; Bouyssi D; Monteiro N Copper-Catalyzed Double C–H Alkylation of Aldehyde-Derived *N,N*-Dialkylhydrazones with Polyhalomethanes: Flexible Access to 4-Functionalized Pyrazoles. ACS Catal. 2016, 6, 7197–7201.(b)Fan X-W; Lei T; Zhou C; Meng Q-Y; Chen B; Tung C-H; Wu L-Z Radical Addition of Hydrazones by α-Bromo Ketones to Prepare 1,3,5-Trisubstituted Pyrazoles Via Visible Light Catalysis. J. Org. Chem 2016, 81, 7127–7133. [PubMed: 27362866] (c)Cheng J; Xu P; Li W; Cheng Y; Zhu C The Functionalization of a Cascade of C(sp^2)-H/C(sp^3)—H Bonds: Synthesis of Fused Dihydropyrazoles Via Visible-Light Photoredox Catalysis. Chem. Commun 2016, 52, 11901–11904.(d)Zhou N; Liu J; Yan Z; Wu Z; Zhang H; Li W; Zhu C Synthesis of Cyclohexylidenehydrazine-Fused Polycyclics Via a Photocatalytic Radical Cascade Reaction of 2-Ethynylaldehyde Hydrazones. Chem. Commun 2017, 53, 2036–2039.(e)Cheng J; Li W; Duan Y; Cheng Y; Yu S; Zhu C Relay Visible-Light Photoredox Catalysis: Synthesis of Pyrazole Derivatives Via Formal [4 + 1] Annulation and Aromatization. Org. Lett 2017, 19, 214–217. [PubMed: 27996274] (f)Luescher MU; Songsichan T; Hsieh S-Y; Bode JW Copper Promoted Oxidative Coupling of Snap Hydrazines and Aldehydes to Form Chiral 1,4,5-Oxadiazepanes and 1,2,5-Triazepanes. Helv. Chim. Acta 2017, 100, e1700199.

(16) (a). Cheng D; Shen Y; Wu Z; Xu X; Yan J Metal-Free Tandem Oxidative Cyclization for the Synthesis of 1,2-Dihydropyridazines and Pyrazoles. J. Org. Chem 2021, 86, 8563–8575.(b)Fernández M; Uria U; Vicario JL; Reyes E; Carrillo L Enantioselective Conjugate Addition of Donor–Acceptor Hydrazones to α,β-Unsaturated Aldehydes through Formal Diaza–Ene Reaction: Access to 1,4-Dicarbonyl Compounds. J. Am. Chem. Soc 2012, 134, 11872–11875. [PubMed: 22780683] (c)Hashimoto T; Hirose M; Maruoka K Asymmetric Imino Aza-Enamine Reaction Catalyzed by Axially Chiral Dicarboxylic Acid: Use of Arylaldehyde *N,N*-Dialkylhydrazones as Acyl Anion Equivalent. J. Am. Chem. Soc 2008, 130, 7556–7557. [PubMed: 18491901] (d)Kaïm LE; Gautier L; Grimaud L; Harwood LM; Michaut V The Mannich Reaction of Hydrazones: Improved Reactivity under Solvent-Free Conditions. Green Chem. 2003, 5, 477–479.(e)Singh K; Ralhan S; Sharma PK; Dhawan SN Vilsmeier–Haack Reaction on Hydrazones: A Convenient Synthesis of 4-Formylpyrazoles. J. Chem. Res 2005, 2005, 316–318.(f)Xu P; Wang G; Wu Z; li S; Zhu C Rh(III)-Catalyzed Double C–H Activation of Aldehyde Hydrazones: A Route for Functionalized 1H-Indazole Synthesis. Chem. Sci 2017, 8, 1303–1308. [PubMed: 28616139] (g)Xu X; Zavalij PY; Hu W; Doyle MP Vinylogous Reactivity of Enol Diazoacetates with Donor–Acceptor Substituted Hydrazones. Synthesis of Substituted Pyrazole Derivatives. J. Org. Chem 2013, 78, 1583–1588. [PubMed: 23301562] (h)Zabaleta N;

Uria U; Reyes E; Carrillo L; Vicario JL Ion-Pairing Catalysis in the Enantioselective Addition of Hydrazones to N-Acyldihydropyrrole Derivatives. Chem. Commun 2018, 54, 8905–8908.

(17) (a). Blackwell JH; Kumar R; Gaunt MJ Visible-Light-Mediated Carbonyl Alkylative Amination to All-Alkyl α-Tertiary Amino Acid Derivatives. J. Am. Chem. Soc 2021, 143, 1598–1609. [PubMed: 33428383] (b)Aguilar Troyano FJ; Merkens K; Anwar K; Gómez-Suárez A Radical-Based Synthesis and Modification of Amino Acids. Angew. Chem., Int. Ed 2021, 60, 1098–1115.

(18) (a). Chuentragool P; Kurandina D; Gevorgyan V Catalysis with Palladium Complexes Photoexcited by Visible Light. Angew. Chem., Int. Ed 2019, 58, 11586–11598.(b)Zhou W-J; Cao G-M; Zhang Z-P; Yu D-G Visible Light-Induced Palladium-Catalysis in Organic Synthesis. Chem. Lett 2019, 48, 181–191.

(19) (a). McMahon CM; Alexanian EJ Palladium-Catalyzed Heck-Type Cross-Couplings of Unactivated Alkyl Iodides. Angew. Chem., Int. Ed 2014, 53, 5974–5977.(b)Zou Y; Zhou J Palladium-Catalyzed Intermolecular Heck Reaction of Alkyl Halides. Chem. Commun 2014, 50, 3725–3728.(c)McAtee JR; Yap GPA; Watson DA Rational Design of a Second Generation Catalyst for Preparation of Allylsilanes Using the Silyl-Heck Reaction. J. Am. Chem. Soc 2014, 136, 10166–10172. [PubMed: 25003502] (d)Reid WB; Spillane JJ; Krause SB; Watson DA Direct Synthesis of Alkenyl Boronic Esters from Unfunctionalized Alkenes: A Boryl-Heck Reaction. J. Am. Chem. Soc 2016, 138, 5539–5542. [PubMed: 27104749]

(20) (a). Kurandina D; Chuentragool P; Gevorgyan V Transition-Metal-Catalyzed Alkyl Heck-Type Reactions. Synthesis 2019, 51, 985–1005. [PubMed: 31666755] (b)Lee GS; Kim D; Hong SH Pd-Catalyzed Formal Mizoroki–Heck Coupling of Unactivated Alkyl Chlorides. Nat. Commun 2021, 12, 991. [PubMed: 33579940] (c)Zhang Z; Kvasovs N; Dubrovina A; Gevorgyan V Visible Light Induced Brønsted Acid Assisted Pd-Catalyzed Alkyl Heck Reaction of Diazo Compounds and N-Tosylhydrazones. Angew. Chem., Int. Ed 2022, 61, e202110924.(d)Zhao B; Shang R; Wang G-Z; Wang S; Chen H; Fu Y Palladium-Catalyzed Dual Ligand-Enabled Alkylation of Silyl Enol Ether and Enamide under Irradiation: Scope, Mechanism, and Theoretical Elucidation of Hybrid Alkyl Pd(I)-Radical Species. ACS Catal. 2020, 10, 1334–1343. (e)Kancherla R; Muralirajan K; Maity B; Zhu C; Krach PE; Cavallo L; Rueping M Oxidative Addition to Palladium(0) Made Easy through Photoexcited-State Metal Catalysis: Experiment and Computation. Angew. Chem., Int. Ed 2019, 58, 3412–3416.

(21). Kvasovs N; Iziumchenko V; Palchykov V; Gevorgyan V Visible Light-Induced Pd-Catalyzed Alkyl-Heck Reaction of Oximes. ACS Catal. 2021, 11, 3749–3754. [PubMed: 34422448]

(22). Saeed A; Ifzan Arshad M; Bolte M; Fantoni AC; Delgado Espinoza ZY; Erben MF On the Roles of Close Shell Interactions in the Structure of Acyl-Substituted Hydrazones: An Experimental and Theoretical Approach. Spectrochim. Acta A Mol. Biomol. Spectrosc 2016, 157, 138–145. [PubMed: 26761413]

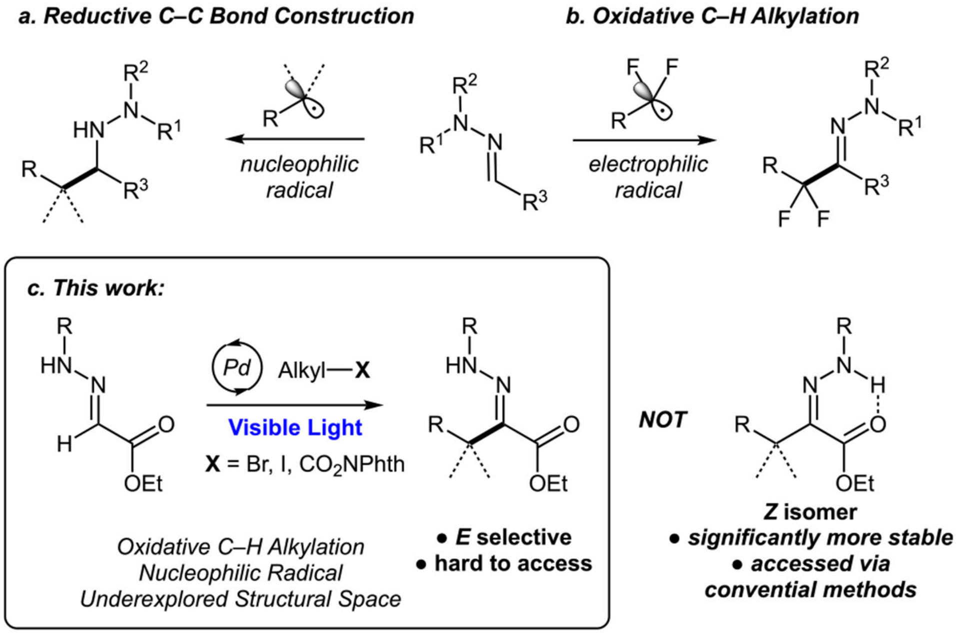
(23) (a). Isar P; Ravikanth M Facile Synthesis of Fused Oxasapphyrins. Org. Lett 2019, 21, 9502–9505. [PubMed: 31725309] (b)Prieto A; Bouyssi D; Monteiro N Copper-Catalyzed Trifluoromethylation of Hydrazones Leading to the Formation of Quaternary α-Trifluoromethyl Diazenes. Asian J. Org. Chem 2016, 5, 742–745.

(24) (a). Yasui E; Wada M; Takamura N Novel Approach to Arylhydrazones, the Precursor for Fischer Indole Synthesis, Via Diazo Esters Derived from α-Amino Acid Esters. Tetrahedron Lett. 2006, 47, 743–746.(b)Yasui E; Wada M; Takamura N Novel Method for Synthesis of Aryl Hydrazones from α-Diazo Esters: Scope and Limitations of Nucleophiles. Tetrahedron 2009, 65, 461–468.

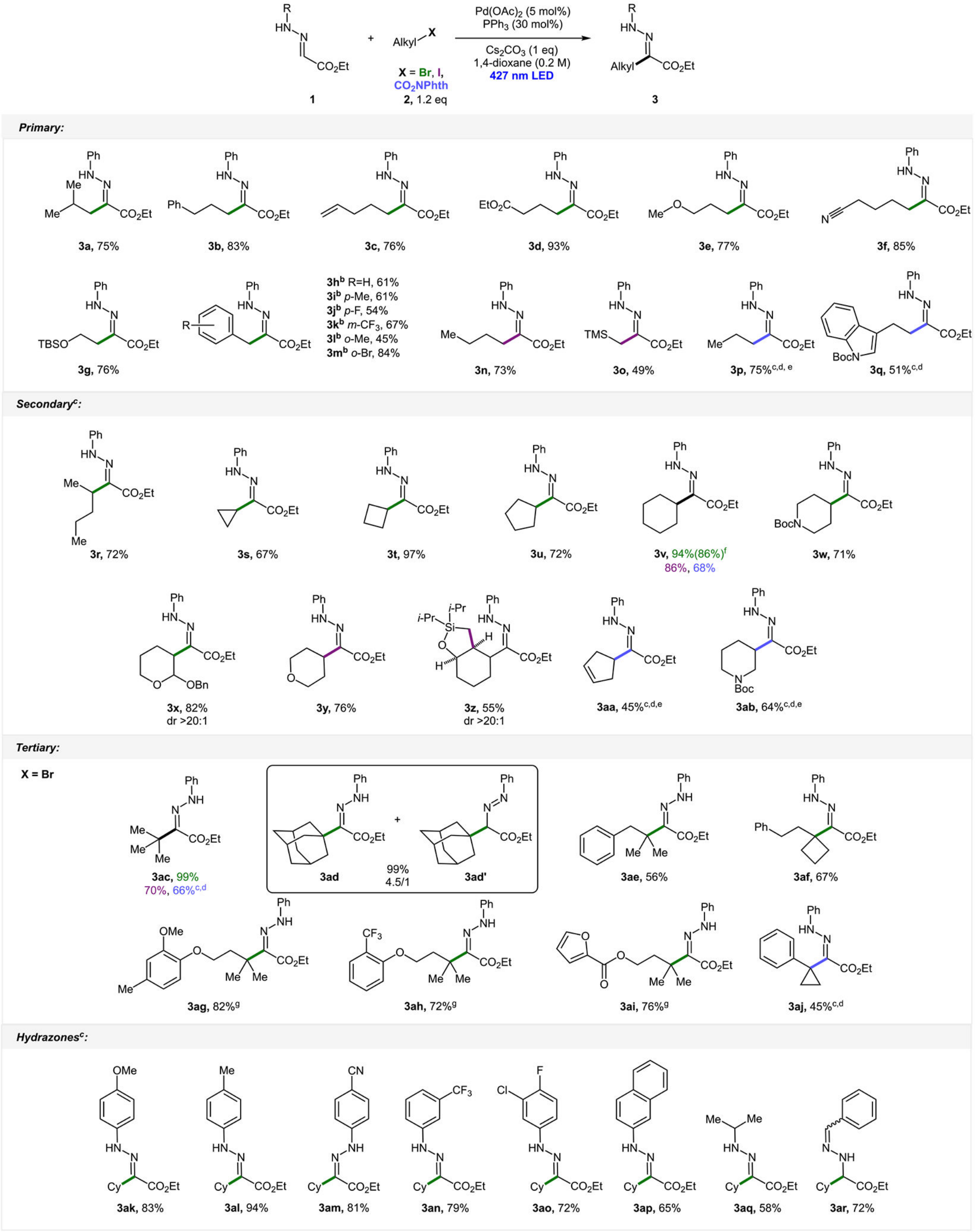
(25). Sakakura T; Hara M; Tanaka M Reaction of Silyl Enol Ethers with Arenediazonium Salts. Part 2. α-Amination of Esters. J. Chem. Soc., Perkin Trans 1 1994, 289–293.

(26). See the Supporting Information for details.

(27) (a). Pantaine LRE; Milligan JA; Matsui JK; Kelly CB; Molander GA Photoredox Radical/Polar Crossover Enables Construction of Saturated Nitrogen Heterocycles. Org. Lett 2019, 21, 2317–2321. [PubMed: 30860849] (b)Slater KA; Friestad GK Mn-Mediated Radical-Ionic Annulations of Chiral N-Acylhydrazones. J. Org. Chem 2015, 80, 6432–6440. [PubMed: 25992979]

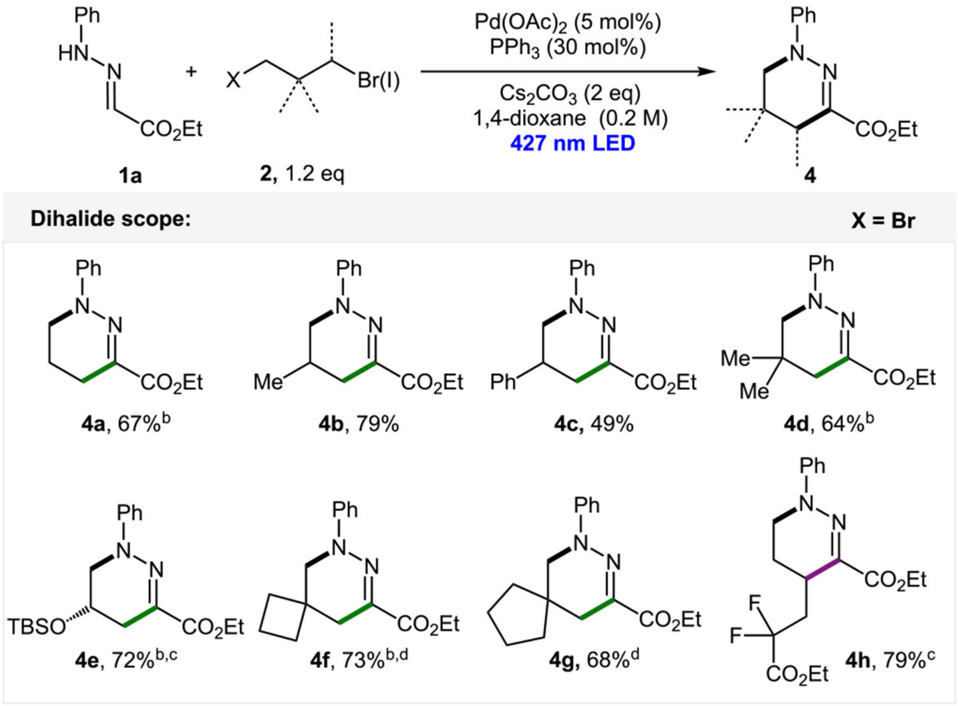


Scheme 1. Radical Reactions of Hydrazones



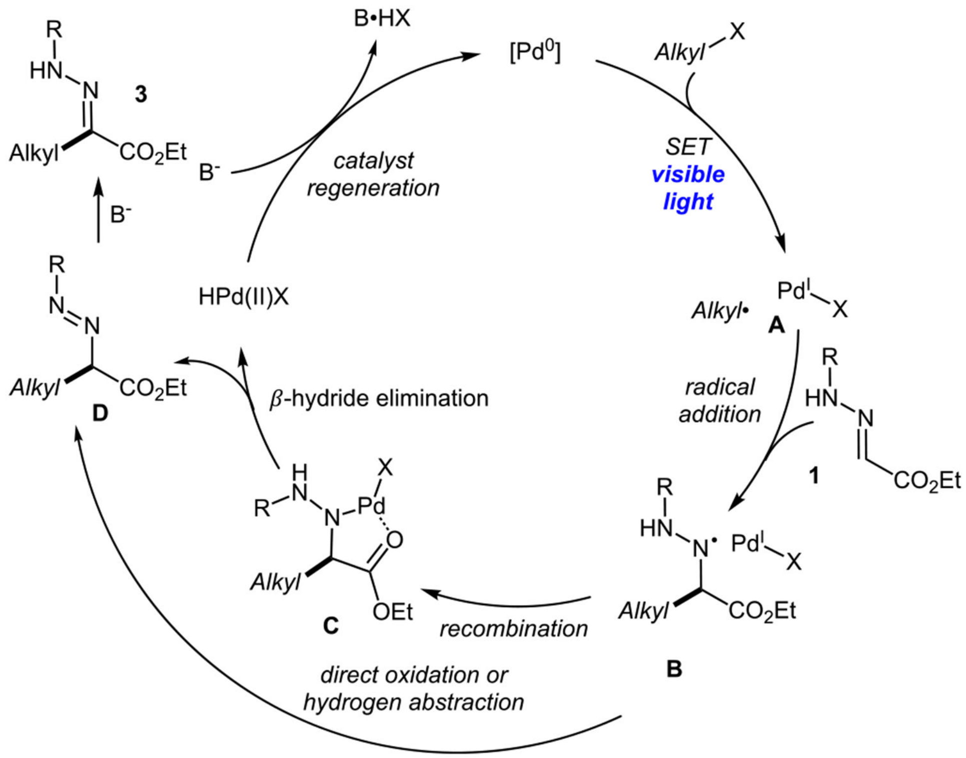
Scheme 2. Scope of Hydrazone in the Alkylation Reaction[a]

[a]At a 0.3 mmol scale. [b]Xantphos (15 mol %) was used instead of PPh_3. [c]Hexamethylphosphoramide (HMPA, 0.2 M) was used as a solvent (if X = Br). [d]$Pd(PPh_3)_4$ (5 mol %) was used instead of $Pd(OAc)_2/PPh_3$. [e]A 1.5 equiv of redox-active ester used. [f]A 2 mmol scale yield. [g]A 1 equiv of tertiary bromide and 1.2 equiv of compound **1**.



Scheme 3. Scope of the Sequential C,N-Alkylation Reaction[a]

[a]At a 0.3 mmol scale. [b]1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base. [c]X = Cl. [d]A 1.5 equiv of dibromide.



Scheme 4. Proposed Reaction Mechanism