

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

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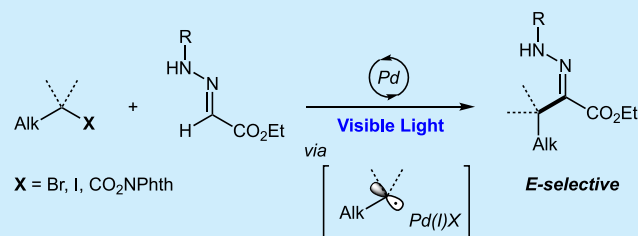


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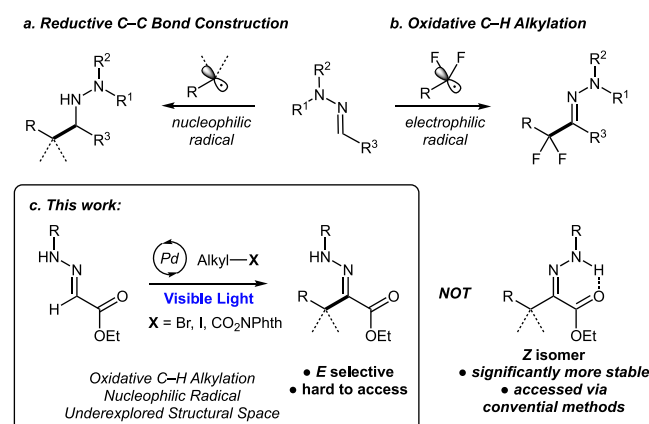
ABSTRACT: A visible-light-induced Pd-catalyzed stereoselective synthesis of alkylated ester hydrazones has been developed. This method operates via generation of a nucleophilic carbon-centered radical from alkyl bromide, iodide, or redox-active ester, followed by its addition to hydrazone, and a subsequent 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.



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 pyrazoles¹ and indoles,² as well as in azaenolate reactions³ and carbene chemistry.⁴ Beyond synthetic chemistry, hydrazones are used in bioconjugation,⁵ polymer,⁶ and material⁷ 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, 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-

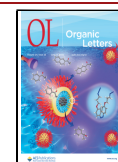
fluorinated radical examples present in the literature,¹⁵ which means that, even though oxidative C–H alkylation is possible, it remains quite limited in the choice of radical precursors to date. In addition, these reactions most often rely on use of dialkyl-substituted hydrazones, which may prevent 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

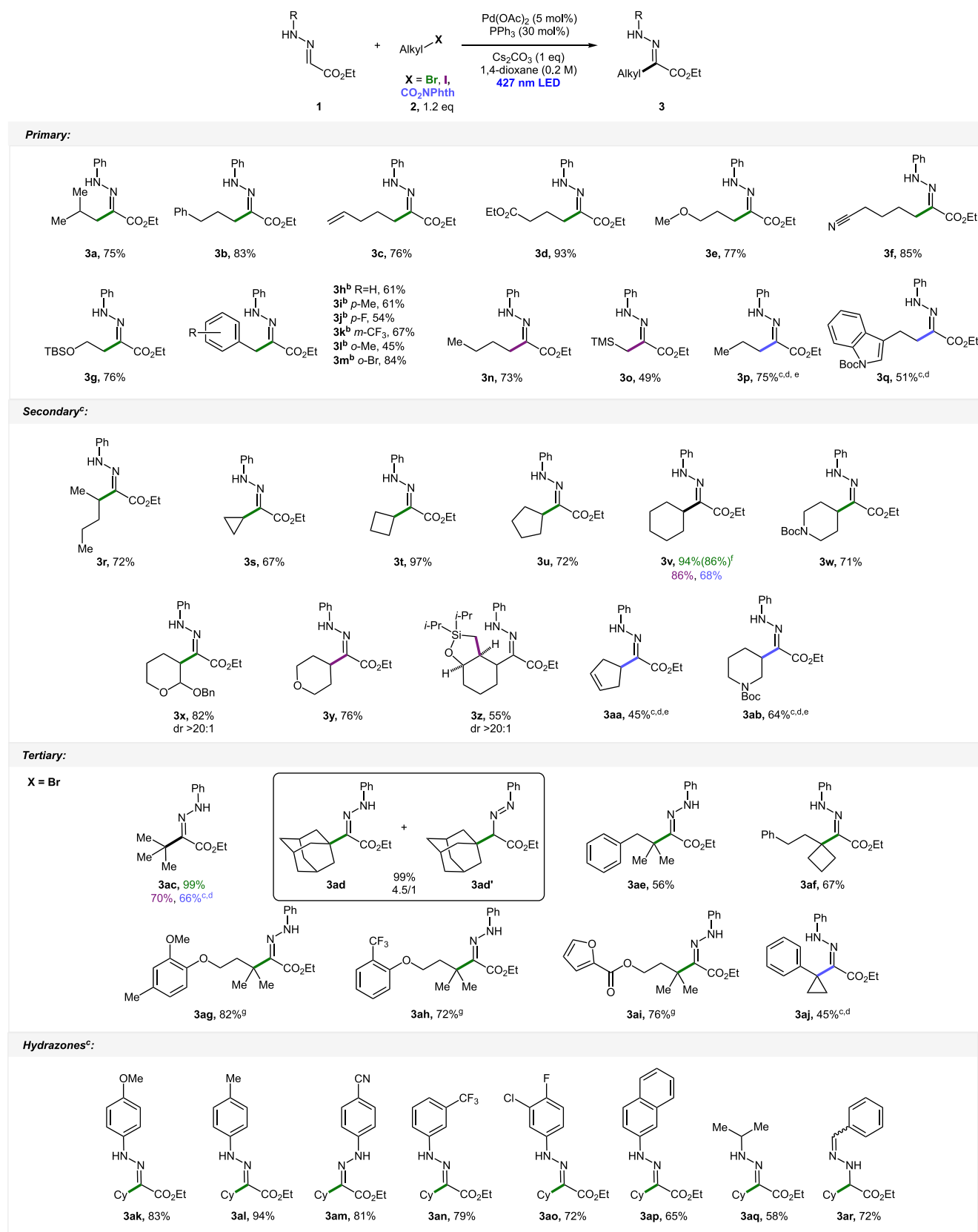
Scheme 1. Radical Reactions of Hydrazones



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Scheme 2. Scope of Hydrazone in the Alkylation Reaction^a

^aAt a 0.3 mmol scale. ^bXantphos (15 mol %) was used instead of PPh₃. ^cHexamethylphosphoramide (HMPA, 0.2 M) was used as a solvent (if X = Br). ^dPd(PPh₃)₄ (5 mol %) was used instead of Pd(OAc)₂/PPh₃. ^eA 1.5 equiv of redox-active ester used. ^fA 2 mmol scale yield. ^gA 1 equiv of tertiary bromide and 1.2 equiv of compound 1.

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-type¹⁹ transformations of styrenes and other activated alkenes²⁰ and oximes²¹ 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.

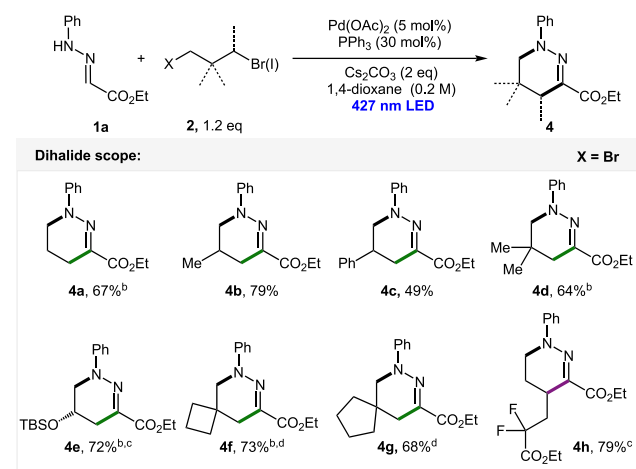
A set of conditions was identified for coupling hydrazone **1** with cyclohexyl bromide **2** (see the Supporting Information for details). Surprisingly, the obtained product had an *E* configuration, despite the fact that the *Z* isomer is significantly more thermodynamically stable as a result of internal 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 compounds²⁴ or silyl-enol ethers with diazonium salts²⁵ 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 trimethylsilylmethylene 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 CDCl₃.²⁶ 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-

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

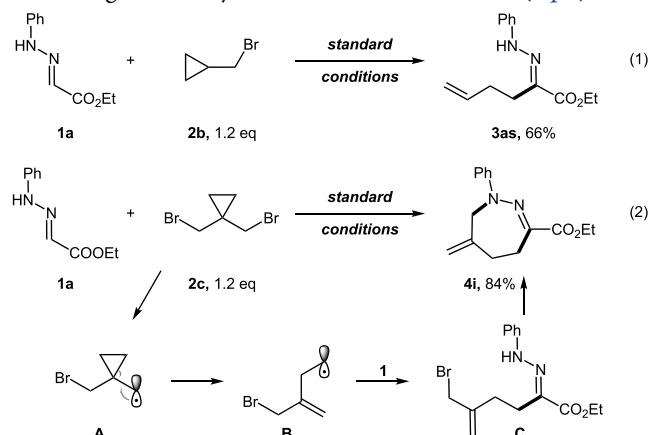


^aAt a 0.3 mmol scale. ^b1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base. ^cX = Cl. ^dA 1.5 equiv of dibromide.

membered heterocycles were synthesized, including the phenyl-substituted product (**4c**), (*S*)-epichlorohydrin derivative (**4e**), 4,6- and 5,6-spirocycles (**4f** and **4g**), and difluoro-containing product (**4h**).

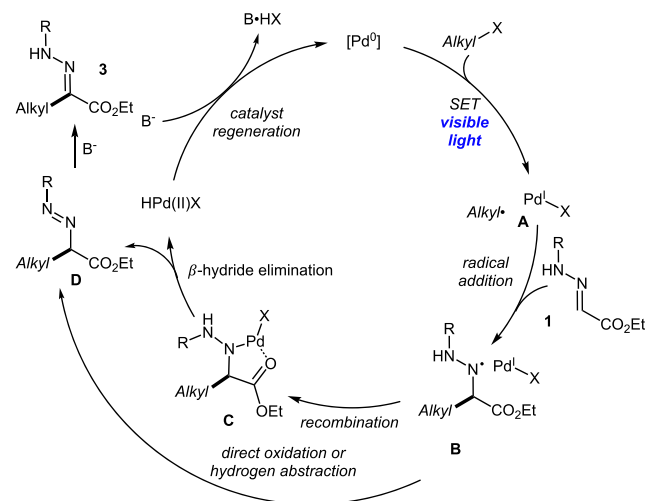
The formation of the carbon-centered radical was validated by reactions of (bromomethyl)cyclopropane under standard reaction conditions, which led to a ring-opening product **3as** in a moderate yield (eq 1). Notably, when bis(bromomethyl)-

cyclopropane **2c** was employed, a seven-membered heterocycle containing an endocyclic alkene **4i** was obtained (eq 2).



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-

Scheme 4. Proposed Reaction Mechanism



induced alkyl Pd hybrid species **A** is produced, followed by the favorable¹⁰ 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.

■ ASSOCIATED CONTENT

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)

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Notes

The authors declare no competing financial interest.

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