

On the Use of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as Catalyst for the Synthesis of Hydrazones Derived from Aromatic Aldehydes and Ketones [†]

Didier F. Vargas *, Brenda S. Romero, Teodoro S. Kaufman and Enrique L. Larghi *

Instituto de Química Rosario IQUIR (CONICET-UNR), and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario (UNR), Suipacha 531, 2000 Rosario, Argentina; kaufman@iquir-conicet.gov.ar (T.S.K.)

* Correspondence: vargas@iquir-conicet.gov.ar (D.F.V.); larghi@iquir-conicet.gov.ar (E.L.L.)

[†] Presented at the 24th International Electronic Conference on Synthetic Organic Chemistry, 15 November–15 December 2020; Available online: <https://ecsoc-24.sciforum.net/>.

Received: date; Accepted: date; Published: date

Abstract: Hydrazoneation of acetophenones and benzaldehydes under CeCl_3 -assistance was evaluated. The transformations entailed the use of the respective hydrazines ($\text{H}_2\text{N-NH}_2 \cdot \text{HCl}$, $\text{Me}_2\text{N-NH}_2$ or $\text{Ph}_2\text{N-NH}_2 \cdot \text{HCl}$) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2–5 mol%). The use of different solvents in a model reaction between 3,4-dimethoxybenzaldehyde and *N,N*-dimethylhydrazine was studied.

Keywords: hydrazoneation; hydrazones; CeCl_3 -assisted reaction

1. Introduction

Hydrazones are a class of organic compounds with the structure, $\text{R}^1\text{R}^2\text{C}=\text{N-NR}^3\text{R}^4$ (Figure 1). These prominent compounds have been widely used in bioconjugation and functionalization of polymers; due to the ease of introducing these functions into biomolecules and probes [1], hydrazones have exerted a dominant influence in many other research areas as well. For example, these compounds have been used extensively in materials science for the synthesis of molecular switches [2], hydrogels [3], sensors, and fluorophores [4].

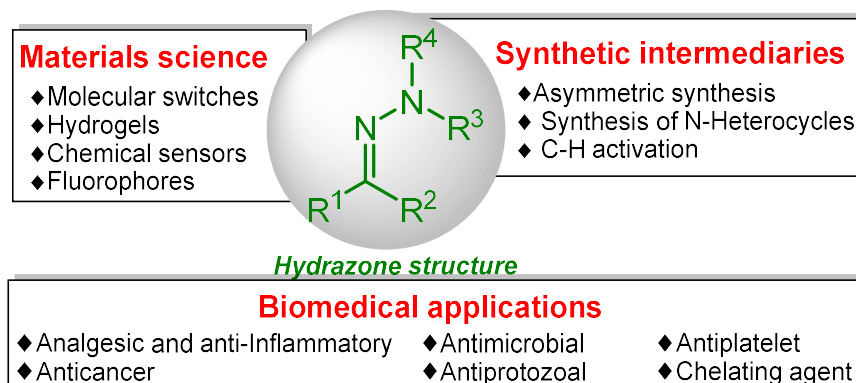


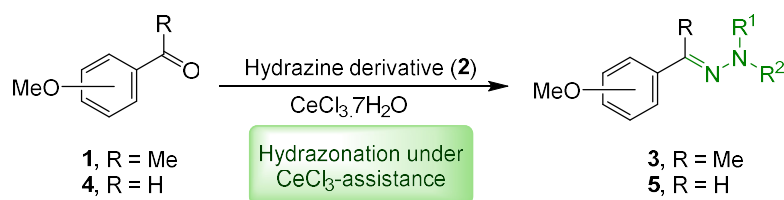
Figure 1. General structure and applications of hydrazones.

Other characteristics of the hydrazones are their diverse biomedical applications [5] and their utility as high value synthetic intermediates in asymmetric synthesis [6], synthesis of N-heterocycles [7] and C-H activation [8]. Indeed, these types of scaffolds are key intermediaries in a variety of chemical transformations and can be classified as versatile building blocks for organic synthesis.

Therefore, development of new synthetic approaches to such compounds is considered of high relevance.

On the other hand, the synthesis of hydrazones is mainly carried out by a reaction between hydrazine derivatives and aldehydes/ketones under promotion of Brønsted acids [9] in a protic solvent or through the use of a Dean-Stark trap [10], that usually requires long heating times. Particularly, Lewis acids have been seldom employed for their preparation [11].

Recently, our group reported the use of oximes as synthetic intermediates for the total synthesis of natural isoquinolines [12,13]. The formation of these oximes was carried out through the use of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as an efficient and eco-friendly promoter, as developed by Cortés et al. [14]. Against this background, we have studied CeCl_3 -assisted hydrazonation of acetophenones and benzaldehydes in order to explore a new eco-friendly approach to this reaction (Scheme 1).

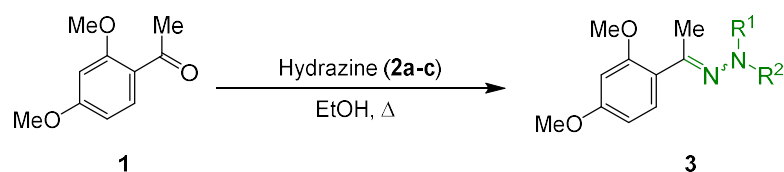


Scheme 1. CeCl_3 -assisted hydrazonation of acetophenones and benzaldehydes.

2. Results and Discussion

In the synthesis of 6-*O*-methyl ancistrochicine, an alkaloid isolated from *Ancistrocladus tectorius*, it was projected to use the hydrazones **3** as potential *ortho*-directing substrates in the $\text{C}(\text{sp}^2)\text{-H}$ activation reaction [13]. For the preparation of these compounds, 2,4-dimethoxyacetophenone (**1**) was subjected to hydrazonation with hydrazine hydrochloride **2a** ($\text{H}_2\text{N-NH}_2 \cdot \text{HCl}$), *N,N*-dimethylhydrazine **2b** ($\text{Me}_2\text{N-NH}_2$) and *N,N*-diphenylhydrazine hydrochloride **2c** ($\text{Ph}_2\text{N-NH}_2 \cdot \text{HCl}$) in EtOH at reflux for 24 h, to provide good isolated yields (63–80%) of the expected hydrazones **3a–c** (Table 1, entries 1, 3 and 5).

Table 1. Preparation of acetophenone derived hydrazones (**3a–c**).



Entry	R ¹	R ²	Hydrazine (Equiv.)	Additive (Equiv.)	t (h)	Yield (%) ^a
1	H	H	$\text{H}_2\text{NNH}_2 \cdot \text{HCl}$ (2.0)	NaOAc (2.5)	24	74
2	H	H	$\text{H}_2\text{NNH}_2 \cdot \text{HCl}$ (2.0)	NaOAc (2.5), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.05)	12	20
3	Me	Me	Me_2NNH_2 (2.5)	AcOH (1.5)	24	63
4	Me	Me	Me_2NNH_2 (2.5)	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.05)	12	15
5	Ph	Ph	$\text{Ph}_2\text{NNH}_2 \cdot \text{HCl}$ (2.0)	NaOAc (2.5)	24	80
6	Ph	Ph	$\text{Ph}_2\text{NNH}_2 \cdot \text{HCl}$ (2.0)	NaOAc (2.5), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.05)	12	58

^a These compounds were obtained as mixtures of *E* and *Z* isomers.

In this same work, we were interested in evaluating the assistance of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in these reactions (Table 1, entries 2, 4 and 6). Interestingly enough, application of the cerium(III)-assisted protocol to the preparation of the acetophenone hydrazones proved to be an unsuitable alternative, since hydrazones **3a–c** were obtained with lower yields of 20%, 15% and 58%, respectively. This decrease in yields could be related to the hydrolytic instability of hydrazones derived from

acetophenone with respect to the H₂O molecules from the Ce(III) salt, as well as the assistance of CeCl₃ in their hydrolysis [15].

On the other hand, *E/Z* geometric isomers of hydrazones **3a–c** were determined by ¹H NMR analysis and NOE experiments on the hydrazones revealed signal enhancement between the protons of the methyl (**3b**) and *o*-phenyl (**3c**) substituents and H-6, suggesting a plausible *Z*-configuration for their major stereoisomers [16].

The unexpected geometry observed could be attributed to electronic factors of the substituents at both ends of the N–N bond [17]. Therefore, in order to validate our hypothesis, a computational study of the conformations of the hydrazones was carried out. The conformational analysis of *E* and *Z* isomers of hydrazones **3a–c** revealed the most stable conformer; fully optimized structures of *E* and *Z* isomers are shown in Figure 2.

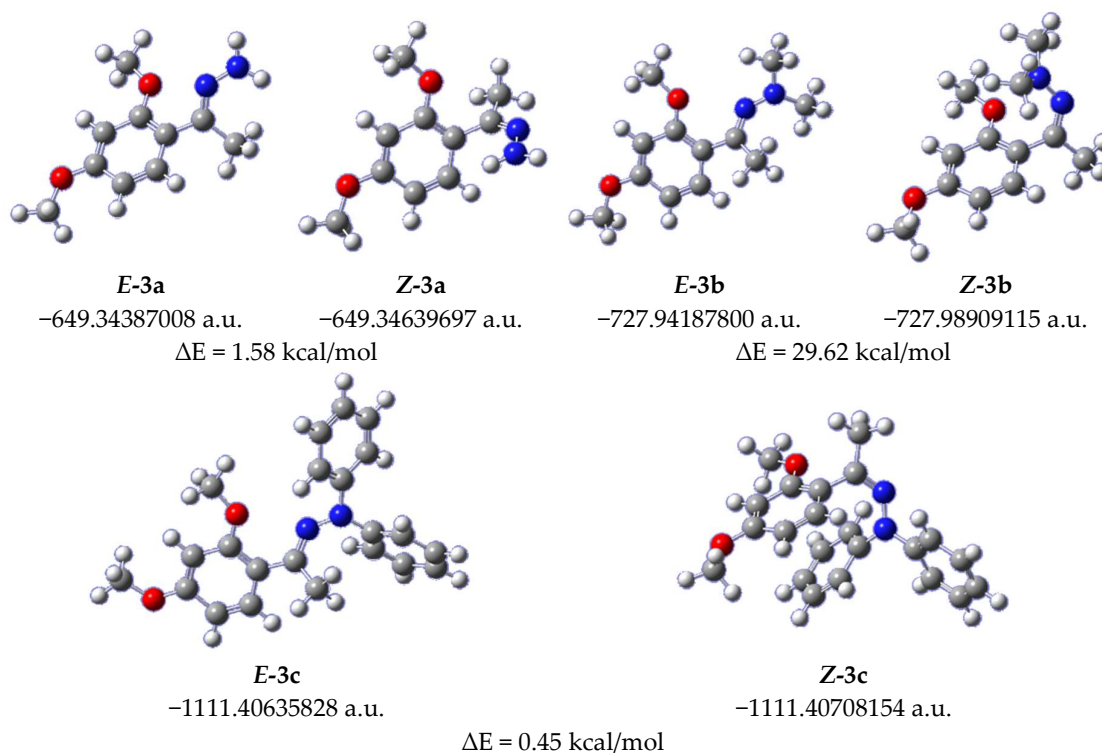


Figure 2. Optimized geometrical structures and calculated total energies (Hartree) of hydrazones **3a–c** at B3LYP/6-31G(d) level of theory.

The lowest energy conformers presented a twisted geometry to avoid steric repulsions between the phenyl ring and the =N–NR₂ group. In all three cases, the results of energy analysis showed that the *Z*-isomers (i.e., the conformers with the lowest total energy resulting from the B3LYP/6-31G(d) calculations for the gas-phase) are more stable than the corresponding lowest-energy *E*-isomers.

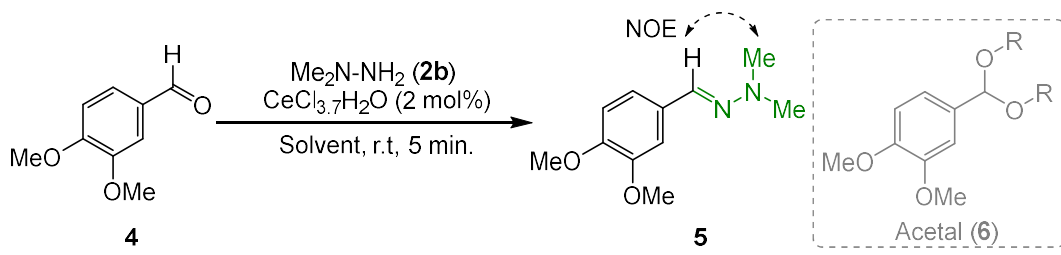
The energy differences between the *E* and *Z* isomers found for the hydrazones **3a** and **3b** were 1.58 and 29.62 kcal/mol, respectively. Nevertheless, for hydrazone **3c** this difference is smaller (0.45 kcal/mol). Thus, the DFT calculations predicted a higher stability for the *Z*-isomers compared to the corresponding *E*-isomers, which is in agreement with the NOE experiments performed on acetophenone hydrazones **3a–c** [13].

On the other side, the performance of the reaction between 3,4-dimethoxy benzaldehyde (**4**) and *N,N*-dimethylhydrazine (**2b**) under CeCl₃·7H₂O-assistance (2 mol%) for the formation of *N,N*-dimethylhydrazone **5** was also evaluated (Table 2). The hydrazoneation was carried out in different solvents at room temperature, affording (*E*)-**5** in 14–97% yield, after stirring for only 5 min [18].

In some cases, minor amounts of the starting material and the formation of acetals (**6**) as undesired products were detected (Table 2, entries 1–3), as an unfavourable effect of the solvent

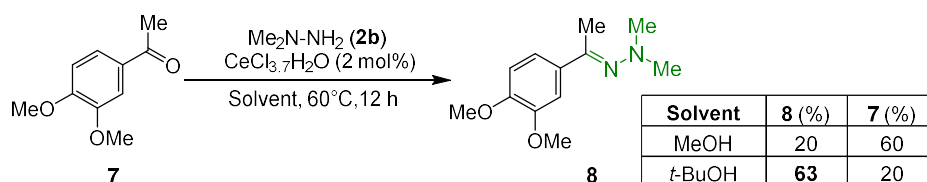
related to its nucleophilicity, and the possible assistance of cerium(III) in the acetalization reaction. For example, the diethyl acetal (R = Et) was isolated with a yield of 22% (Table 2, entry 2) and its structure was confirmed by ^1H NMR analysis where it exhibited a characteristic singlet corresponding to the methine hydrogen [$-\text{CH}(\text{OEt})$] at $\delta = 5.42$ ppm. Rewardingly, the best condition found for this transformation was when *tert*-butanol was employed as solvent (Table 2, entry 4).

Table 2. Screening conditions for the formation of *N,N*-dimethylhydrazone (5).



Entry	Solvent	5 (%)	4 (%)	Acetal (%)
1	MeOH	79	6	traces
2	EtOH	71	4	22
3	<i>i</i> -PrOH	81	16	traces
4	<i>t</i> -BuOH	97	0	0
5	THF	14	63	0
6	MeCN	31	53	0

Furthermore, this protocol was tested for the formation of the *N,N*-dimethylhydrazone of an acetophenone (Scheme 2). Initially, 3,4-dimethoxyacetophenone (7) was subjected to hydrazonation with *N,N*-dimethylhydrazine (2b) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2 mol%) in methanol at room temperature for up to 24 h without showing product formation. After heating at 60 °C for 12 h, only 20% of *N,N*-dimethylhydrazone 8 was isolated; however, with the use of *tert*-butanol the yield was increased to 63%.



Scheme 2. Preparation of acetophenone hydrazones 8.

In general, the results suggest that this protocol could be an advantageous alternative for the formation of aldehyde hydrazones, while the preparation of acetophenone derivatives may require more drastic conditions and the use of specific solvents like *t*-BuOH.

3. Experimental Section

3.1. General Experimental Details

The reactions were monitored by TLC, using silica gel GF₂₅₄ plates supported on aluminium and run in different hexane-EtOAc solvent mixtures containing Et₃N (1% *v/v*). The chromatographic spots were detected by exposure of the plates to 254 nm UV light, and by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent. The flash column chromatographies were run with silica gel 60 H (particle size < 55 μm), eluting with hexane-EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques.

The nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 NMR spectrometer, at 300.13 (^1H) and 75.48 (^{13}C) MHz. CDCl_3 was used as solvent, and the chemical shifts are informed in parts per million (ppm) in the δ scale. TMS was used as the internal standard (resonances of CHCl_3 in CDCl_3 : δ 7.26 and 77.0 ppm for ^1H and ^{13}C NMR, respectively).

3.2. General Procedure for the Preparation of *N,N*-Dimethylhydrazones

A mixture of the corresponding carbonyl compound (0.2 mmol), *N,N*-dimethyl hydrazine (0.25 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (0.004 mmol) in *tert*-butanol (1 mL) was stirred or heated until complete consumption of the starting material was observed. The solvent was then evaporated and the residue was purified by column chromatography, to afford the corresponding *N,N*-dimethylhydrazones.

3.3. Computational Details

Initially, a conformational search was performed using the corresponding module of HyperChem v. 8.0 with the MM+ method. Then the selected structures were used as input geometries for the Gaussian-09 program package and successively re-optimized by using the density functional theory (DFT) at the B3LYP/6-31G(d) level of theory. The selected geometries of these rotamers correspond to the energy minima in the gas-state.

4. Conclusions

An efficient method for the preparation of *N,N*-dimethylhydrazones was developed. We have collected evidence on the assistance of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in the hydrazoneation of 3,4-dimethoxybenzaldehyde with *N,N*-dimethylhydrazine, which resulted in a shortened reaction time, when compared with previous protocols. A visible solvent effect was observed during the preparation of *N,N*-dimethylhydrazones derived from benzaldehyde. On the other hand, this protocol was not so efficient when acetophenones such as 3,4-dimethoxyacetophenone were reacted with *N,N*-dimethylhydrazine.

Acknowledgments: The authors gratefully acknowledge Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET, PUE IQUIR-2016) and Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT, PICT 2018-01933 and PICT 2017-0149) for financial support. D. F. V. also thanks CONICET for his fellowship.

References

1. Kölmel, D.K.; Kool, E.T. Oximes and hydrazones in bioconjugation: Mechanism and catalysis. *Chem. Rev.* **2017**, *117*, 10358–10376, doi:10.1021/acs.chemrev.7b00090.
2. Su, X.; Aprahamian, I. Hydrazone-based switches, metallo-assemblies and sensors. *Chem. Soc. Rev.* **2014**, *43*, 1963–1981, doi:10.1039/c3cs60385g.
3. Sharma, P.K.; Singh, Y. Glyoxylic hydrazone linkage-based PEG hydrogels for covalent entrapment and controlled delivery of doxorubicin. *Biomacromolecules* **2019**, *20*, 2174–2184, doi:10.1021/acs.biomac.9b00020.
4. Tatum, L.A.; Su, X.; Aprahamian, I. Simple hydrazone building blocks for complicated functional materials. *Acc. Chem. Res.* **2014**, *47*, 2141–2149, doi:10.1021/ar500111f.
5. (a) Wahbeh, J.; Milkowski, S. The use of hydrazones for biomedical applications. *SLAS Technol. Transl. Life Sci. Innov.* **2019**, *24*, 161–168, doi:10.1177/2472630318822713; (b) Verma, G.; Marella, A.; Shaquiquzzaman, M.; Akhtar, M.; Ali, M.R.; Alam, M.M. A review exploring biological activities of hydrazones. *J. Pharm. Bioallied Sci.* **2014**, *6*, 69–80, doi:10.4103/0975-7406.129170.
6. De Gracia Retamosa, M.; Matador, E.; Monge, D.; Lassaletta, J.M.; Fernández, R. Hydrazones as singular reagents in asymmetric organocatalysis. *Chem. Eur. J.* **2016**, *22*, 13430–13445, doi:10.1002/chem.201602430.
7. Groenendaal, B.; Ruijter, E.; Orru, R.V.A. 1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles. *Chem. Commun.* **2008**, 5474–5489, doi:10.1039/b809206k.
8. Xu, X.; Zhang, J.; Xia, H.; Wu, J. C(sp²)-H functionalization of aldehyde-derived hydrazones via a radical process. *Org. Biomol. Chem.* **2018**, *16*, 1227–1241, doi:10.1039/C8OB00056E.
9. (a) Mohamady, S.; Kralt, B.; Samwel, S.K.; Taylor, S.D. Efficient one-pot, two-component modular synthesis of 3,5-disubstituted pyrazoles. *ACS Omega* **2018**, *3*, 15566–15574, doi:10.1021/acsomega.8b02304; (b)

- Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. Synthesis of isoquinolines via Rh(III)-catalyzed C–H activation using hydrazone as a new oxidizing directing group. *Org. Lett.* **2013**, *15*, 5750–5753, doi:10.1021/ol402796m.
10. (a) Motiwala, H.F.; Gülgeze, B.; Aubé, J. Copper-catalyzed oxaziridine-mediated oxidation of C–H bonds. *J. Org. Chem.* **2012**, *77*, 7005–7022, doi:10.1021/jo3012336; (b) Dabb, S.L.; Messerle, B.A. Rh(I) and Ir(I) catalysed intermolecular hydroamination with substituted hydrazines. *Dalt. Trans.* **2008**, 6368–6371, doi:10.1039/b814591a.
 11. (a) El-Azab, A.S.; Ghabbour, H.A.; El-Husseiny, W.M.; Maarouf, A.R.; Mohamed, M.A.; Abdel-Aziz, A.A.-M. Lewis acid-promoted direct synthesis of *N*-unsubstituted hydrazones via the reaction of hydrazine with acetophenone and isatin derivatives. *Russ. J. Gen. Chem.* **2016**, *86*, 2837–2844, doi:10.1134/S1070363216120471; (b) dos Santos Filho, J.M. Mild, Stereoselective, and highly efficient synthesis of *n*-acylhydrazones mediated by CeCl₃·7H₂O in a broad range of solvents. *Eur. J. Org. Chem.* **2014**, *2014*, 6411–6417, doi:10.1002/ejoc.201402609.
 12. (a) Fonzo, S.; Vargas, D.F.; Kaufman, T.S. A ruthenium-catalyzed C–H activation strategy as an efficient shortcut in the total synthesis of 6,8-dimethoxy-1,3-dimethylisoquinoline. *Synthesis* **2019**, *51*, 3908–3914, doi:10.1055/s-0037-1610720; (b) Cortés, I.; Borini Etichetti, C.M.; Girardini, J.E.; Kaufman, T.S.; Bracca, A.B.J. Total synthesis and cytotoxic activity of 6,8-dimethoxy-1,3-dimethylisoquinoline isolated from *Ancistrocladus tectorius*: A 6 π -azaelectrocyclization approach. *Synthesis* **2019**, *51*, 433–440, doi:10.1055/s-0037-1610276.
 13. Vargas, D.F.; Romero, B.S.; Larghi, E.L.; Kaufman, T.S. Rhodium(III)-Catalyzed C–H Activation-Based First Total synthesis of 6-*O*-methyl anciscochine, an alkaloid isolated from *Ancistrocladus tectorius*. *Synthesis* **2020**, *52*, 119–126.
 14. Cortés, I.; Kaufman, T.S.; Bracca, A.B.J. A convenient and eco-friendly cerium(III) chloride-catalysed synthesis of methoxime derivatives of aromatic aldehydes and ketones. *R. Soc. Open Sci.* **2018**, *5*, 180279, doi:10.1098/rsos.180279.
 15. Cadav, J.S.; Subba Reddy, B.V.; Reddy, M.S.K.; Sabitha, G. A facile cleavage of ketone *N,N*-dimethylhydrazones by CeCl₃·7H₂O·SiO₂. *Synlett* **2001**, 1134–1136, doi:10.1055/s-2001-15161.
 16. (a) Gergely, J.; Morgan, J.B.; Overman, L.E. Stereocontrolled synthesis of functionalized *cis*-cyclopentapyrazolidines by 1,3-dipolar cycloaddition reactions of azomethine imines. *J. Org. Chem.* **2006**, *71*, 9144–9152, doi:10.1021/jo061537j; (b) Vivona, N.; Frenna, V.; Buscemi, S.; Ruccia, M. Heterocyclic rearrangements. *N,N*-diphenylhydrazones, oximes and *O*-methyloximes of 3-benzoyl-5-phenyl-1,2,4-oxadiazole. *J. Heterocyclic Chem.* **1985**, *22*, 97–99, doi:10.1002/jhet.5570220125.
 17. (a) Vivona, N.; Frenna, V.; Buscemi, S.; Ruccia, M. Heterocyclic rearrangements. *N,N*-Diphenylhydrazones, oximes and *O*-methyloximes of 3-benzoyl-5-phenyl-1,2,4-oxadiazole. *J. Heterocyclic Chem.* **1985**, *22*, 97–99, doi:10.1002/jhet.5570220125; (b) Benassi, R.; Taddei, F. Theoretical study of conformational changes in simple hydrazones. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1629–1632, doi:10.1039/p29850001629.
 18. Ros, A.; López-Rodríguez, R.; Estepa, B.; Álvarez, E.; Fernández, R.; Lassaletta, J.M. Hydrazone as the directing group for Ir-catalyzed arene diborylations and sequential functionalizations. *J. Am. Chem. Soc.* **2012**, *134*, 4573–4576, doi:10.1021/ja300308c.

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



© 2020 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).