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Stereospecific Synthesis of (*E*)-5-Tetrasubstituted-ylidene-3,5-dihydro-4*H*-imidazol-4-ones

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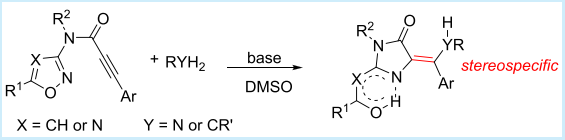
Supporting Information

ABSTRACT: A stereospecific synthesis of (*E*)-5-tetrasubstituted-ylidene-3,5-dihydro-4*H*-imidazol-4-one derivatives is demonstrated through a cascade process by combination of a Michael addition and Boulton−Katritzky rearrangement. The method provides a simple and efficient approach for the synthesis of (*E*)-5-tetrasubstituted-ylidene-3,5-dihydro-4*H*-imidazol-4-ones from the reactions of *N*-(isoxazol-3-yl)-propiolamides or *N*-(1,2,4-oxadiazo-3-yl) propiolamides with N or C nucleophiles.



3,5-Dihydro-5-methylidene-4*H*-imidazol-4-one (MIO) is a key active site for some important aminomutases in the biosynthetic pathways of biologically active compounds in plants and microorganisms.[1] Such a structure has also been found extensively in many bioactive natural products and represents an attractive motif in the development of new drugs and function molecules (Figure 1).[2−4]

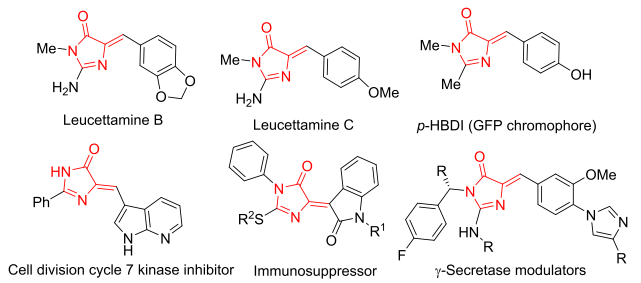
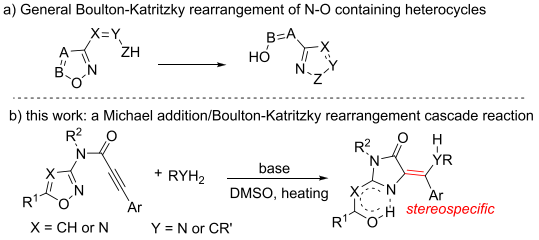


Figure 1. Some examples of bioactive 5-ylidene-3,5-dihydro-4*H*-imidazol-4-one derivatives.

5-Ylidene-3,5-dihydro-4*H*-imidazol-4-ones were generally synthesized through the condensation of corresponding imidazolones with aldehydes or ketones or through different multicomponent reactions from simple substrates.[5] However, the formation of fully substituted double bonds at the 5-position is difficult, and the control of the stereoconfiguration of the double bond is a great challenge in such reactions. Thus, it is extremely desirable to develop novel methods for the highly stereoselective formation of imidazolones with fully substituted 5-position double bonds.

The Boulton−Katritzky rearrangement between two five-membered heterocycles is one of the most investigated ring-transformation reactions and has been extensively applied in the synthesis of a variety of heterocyclic compounds (Scheme 1a).[6,7] Such reactions typically occurred in heterocycles such as isoxazoles[8] and 1,2,4-oxadiazoles,[9] in which the electrophilic N

Scheme 1. Cascade Reaction by Combination of a Michael Addition and Boulton−Katritzky Rearrangement



atom was attacked by nucleophilic side chains and led to the cleavage of the N−O bond and the rearrangement for the formation of more stable five-membered rings.[10] A variety of three-atom side chains have been explored for such rearrangements. However, in most cases, the three-atom side chains need to be preinstalled in the substrates, and normally, N or O was chosen as the nucleophilic group. Only sporadic examples with a C nucleophilic group have been explored.[11]

Our group is interested in the development of novel synthetic methods for the efficient formation of bioactive heterocycles. Recently, we have developed a base-promoted Boulton−Katritzky rearrangement of 1-(isoxazole-3-yl)ureas to 5-(2-oxoalkyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-ones.[12] For a further study, in this work, we would like to disclose our research in combination of a Michael addition and Boulton−Katritzky rearrangement for stereospecific synthesis of (*E*)-5-ylidene-3,5-dihydro-4*H*-imidazol-4-one derivatives (Scheme 1b). In this reaction, a nucleophilic carbon was involved in the rearrangement process.

The reaction of *N*-(5-(*tert*-butyl)isoxazol-3-yl)-*N*-methyl-3-phenylpropiolamide **1a** and $TsNH_2$ **2a** was initiated as a model case. As shown in Table 1, with 1.0 equiv of Cs_2CO_3 as the

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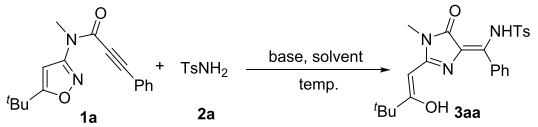
Table 1. Reaction Condition Screening[a]



entry	base (equiv)	solvent	temp (°C)	time (min)	yield (%)[b]
1	Cs_2CO_3 (1.0)	DMSO	120	30	75
2	K_3PO_4 (1.0)	DMSO	120	30	75
3	K_2CO_3 (1.0)	DMSO	120	45	67
4	KO^{t}Bu (1.0)	DMSO	120	30	46
5	NaOEt (1.0)	DMSO	120	30	72
6	NaOH (1.0)	DMSO	120	45	46
7	DMAP (1.0)	DMSO	120	60	12
8	Et3N (1.0)	DMSO	120	60	n.d.[c]
9	DABCO	DMSO	120	60	n.d.[c]
10	K_2CO_3 (0.5)	DMSO	120	45	81
11	Cs_2CO_3 (1.0)	DMSO	100	30	80
12	K_2CO_3 (0.5)	DMSO	100	75	76
13	K_2CO_3 (0.5)	DMF	120	45	63
14	K_2CO_3 (0.5)	THF	70	24 h	57
15	K_2CO_3 (0.5)	dioxane	100	24 h	51
16	K_2CO_3 (0.5)	MeCN	85	8 h	65

[a]Reagents and conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent 2 mL. [b]Isolated yield. [c]Not detected.

base, the reaction proceeded smoothly at 120 °C in DMSO to afford the corresponding product **3aa** in 75% yield in 30 min (Table 1, entry 1). The structure of **3aa** was confirmed through X-ray experiment (Figure 2). The stereoconfiguration of a fully

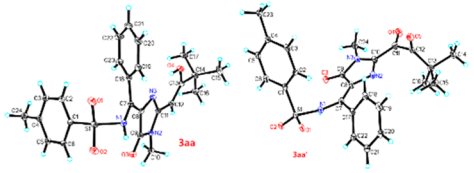
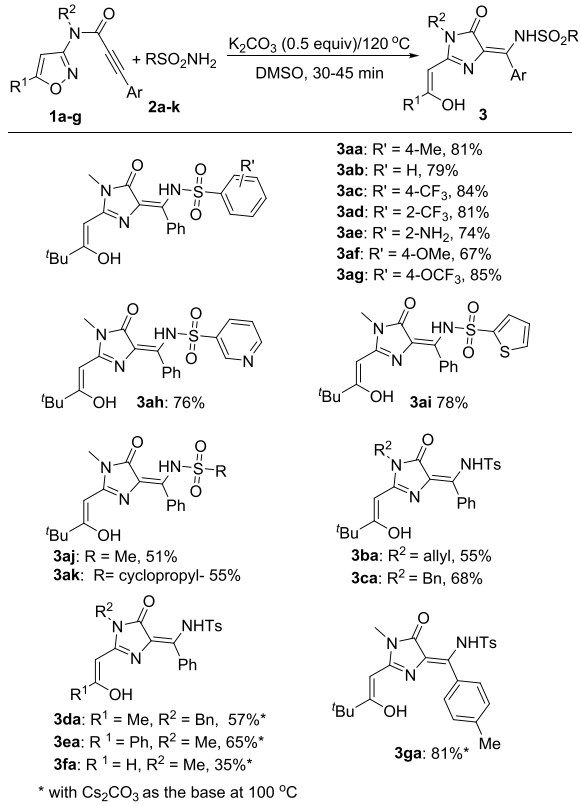


Figure 2. X-ray structures of compounds **3aa** and **3aa′**.

substituted double bond at the 5-position of the 3,5-dihydro-4*H*-imidazol-4-one ring was determined as *E*, which is due to the formation of a hydrogen bond between the oxygen atom of the carbonyl group and NHTs. The double bond of enol was determined as *Z* due to the formation of a hydrogen bond between −OH and the nitrogen atom of the imidazolone. The formations of these two double bonds are very characteristic and made the product structure very attractive. Other bases such as K_3PO_4, K_2CO_3, KO^{t}Bu, NaOEt, and NaOH were also screened, and all delivered the desired product in moderate yield (Table 1, entries 2−6). While organic bases such as DMAP, Et_3N, and DABCO showed poor efficiency (Table 1, entries 7−9), only low yield was obtained with DMAP. Thus, we then took the cheapest K_2CO_3 for further exploration. It revealed that 0.5 equiv of K_2CO_3 is enough to promote the reaction at 120 °C in DMSO, which afforded the product in 81% yield (Table 1, entry 10). A similar result was obtained with 0.5 equiv of Cs_2CO_3 at 100 °C (Table 1, entry 11). Other solvents such as DMF, 1,4-dioxane, THF, or MeCN were also screened at 120 °C or under refluxing, and all the results are inferior to that in DMSO (Table 1, entries 13−16). Noteworthy is that an oxidized diketone side product **3aa′** was detected under prolonged reaction time. The structure of **3aa′** was also confirmed through X-ray experiment (Figure 2). Similar side reactions have been found in our previous research[12] and are also reported in other groups' work.[8c,d]

With the optimized conditions in hand, we then explored the reaction scope with a variety of *N*-(isoxazole-3-yl) propiolamides and sulfonamide substrates. As shown in Scheme 2, different substituent groups, such as methyl,

Scheme 2. Substrate Scope of *N*-(Isoxazo-3-yl)propiolamides with Sulfonamides



methoxy, trifluoromethyl, trifluoromethoxy, and amine, on the aryl rings of aryl sulfonamides were well tolerated, and all delivered the corresponding products in moderate to good results (**3aa**−**3ag**). Heteroaryl sulfonamides such as pyridine-3-sulfonamide and thiophene-2-sulfonamide were also tested and afforded the desired products in high yields (**3ah** and **3ai**). While alkyl-substituted sulfonamides such as methanesulfonamide and cyclopropanesulfonamide were used, the reaction also proceeded well, and the corresponding products **3aj** and **3ak** were obtained in moderate yields. Different substituents of *N*-(isoxazole-3-yl) propiolamides were also well tolerated, and the corresponding products (**3ba**−**3ga**) were delivered in moderate yields.

Further, two *N*-(1,2,4-oxadiazo-3-yl) propiolamides **4a**/**b** and typical sulfonamides were explored in our reactions. As shown in Scheme 3, the reactions proceeded smoothly with Cs_2CO_3 as the base at 100 °C, and all afforded the desired products in good yields. The structure of product **5ba** was determined through X-ray experiment (Figure 3). The characteristic formations of two hydrogen bonds between the oxygen atom of imidazolone with NHTs and the oxygen atom of the side chain with the nitrogen atom of the imidazolone were clearly observed in the structure.

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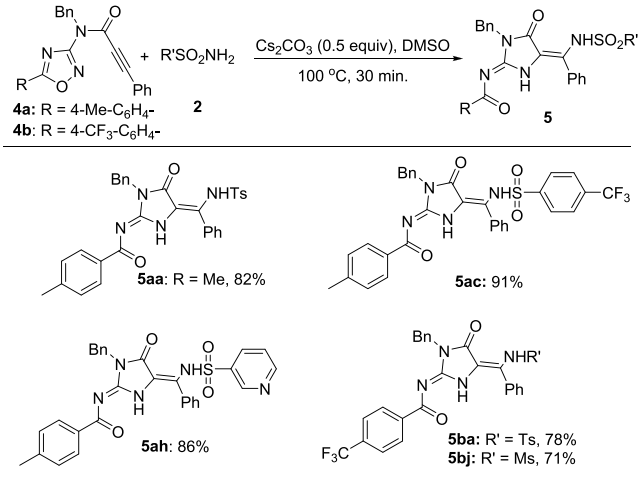
Scheme 3. Substrate Scope of *N*-(1,2,4-Oxadiazo-3-yl)propiolamides with Sulfonamides



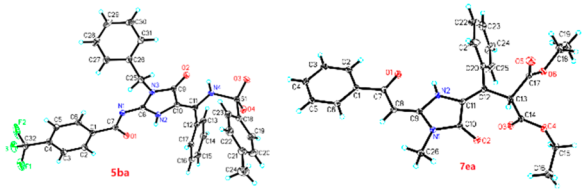
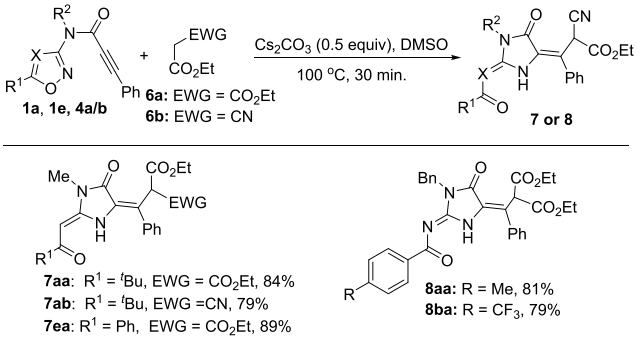


Figure 3. X-ray structures of **5ba** and **7ea**.

To further explore the reaction scope, we chose diethyl malonate **6a** and ethyl 2-cyanoacetate as C-nucleophiles for the cascade reactions. As shown in Scheme 4, the reactions of *N*-

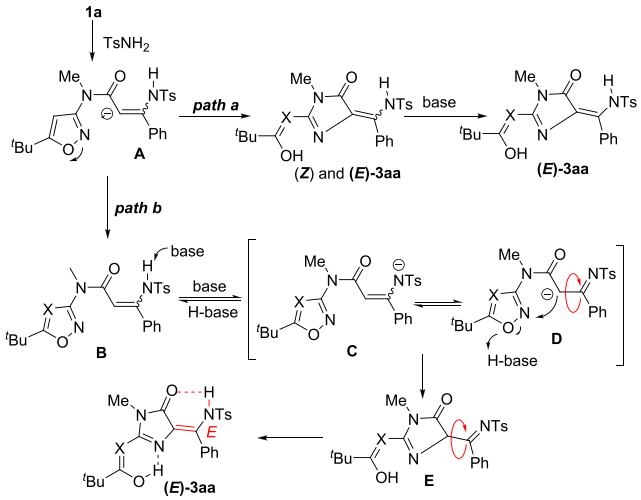
Scheme 4. Exploring a C-Nucleophile for the Cascade Reactions



(isoxazole-3-yl) and *N*-(1,2,4-oxadiazo-3-yl)propiolamides with **6a** or **6b** also worked well and afforded the desired products in good yields. The structure of product **7ea** was confirmed through X-ray experiment (Figure 3).

Two pathways may be possible for the reactions of compound **1a** and $TsNH_2$ as shown in Scheme 5. One is through Michael addition to produce an alkenyl carbanion **A**. The alkenyl carbanion **A** acted as a nucleophilic intermediate to attack the electrophilic N atom of the isoxazoles directly and undergo a Boulton–Katritzky rearrangement to afford the product **3aa** with both (*Z*) and (*E*)-configurations (path a), which may finally convert into thermally more stabilized (*E*)-**3aa** under the basic conditions. Another reasonable pathway (path b) was also proposed. The protonation of intermediate **A** would lead to the formation of intermediate **B** with both (*E*)

Scheme 5. Proposed Mechanism



and (*Z*)-configurations. Intermediate **B** could form an equilibrium with tautomerized intermediates **C** and **D** under basic conditions. Intermediate **D** acted as the nucleophilic intermediate to attack the N atom and undergo the Boulton–Katritzky rearrangement to afford the desired product. The rotation of the single bond during the process and the formation of the hydrogen bond between the oxygen atom of the carbonyl group and NHTs are the key factors accounting for the stereospecificity of the 5-position double bond, while the formation of enol and the stereoconfiguration of the enol double bond are governed by the hydrogen bond between enol OH and the nitrogen atom of the imidazolone.

To confirm the mechanism, a control experiment was performed and shown in Scheme 6. As observed, the reaction

Scheme 6. Control Experiment

of **1a** with *N*-4-dimethylbenzenesulfonamide **9** afforded the Michael addition products **10a**/**10a′**, which are mixtures of *Z* and *E* products. No Boulton–Katritzky rearrangement product was detected. It means that the alkenyl carbanion **A** preferred protonation rather than attacking the electrophilic nitrogen atom to undergo Boulton–Katritzky rearrangement. Since there is no free proton on the nitrogen in **10a**/**10a′**, the following deprotonation and rearrangement could not occur. Thus, the reaction stopped at the Michael addition step. The structure of product (*Z*)-**10a** was confirmed through X-ray experiment, and the (*E*)-product was deduced through NMR data. The control experiment proved that the mechanism through path b is more reasonable for our reactions.

In summary, a stereospecific synthesis of (*E*)-5-tetrasubstituted-ylidene-3,5-dihydro-4*H*-imidazol-4-ones is developed. The method is through a tandem reaction of *N*-(isoxazole-3-yl) or *N*-(1,2,4-oxadiazol-3-yl) propiolamides with sulfonamides or diethyl malonate by combination of a Michael addition and Boulton–Katritzky rearrangement. Further development and applications of this method are ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01063.

Full experimental and characterization data, including ^{1}H and ^{13}C NMR for the products (PDF)

Accession Codes

CCDC 1904658−1904661 and 1905308 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Attanayake, G.; Walter, T.; Walker, K. D. *Biochemistry* **2018**, *57*, 3503−3514. (b) Sanchez-Murcia, P. A.; Bueren-Calabuig, J. A.; Camacho-Artacho, M.; Cortes-Cabrera, A.; Gago, F. *Biochemistry* **2016**, *55*, 5854−5864. (c) Weiser, D.; Bencze, L. C.; Bánóczi, G.; Ender, F.; Kiss, R.; Kókai, E.; Szilágyi, A.; Vértessy, B. G.; Farkas, Ö.; Paizs, C.; Poppe, L. *ChemBioChem* **2015**, *16*, 2283−2288.

(2) (a) Chan, G. W.; Mong, S.; Hemling, M. E.; Freyer, A. Y.; Offen, P. H.; DeBrosse, C. W.; Sarau, H. M.; Westley, J. W. *J. Nat. Prod.* **1993**, *56*, 116−121. (b) Crews, P.; Clark, D. P.; Tenney, K. *J. Nat. Prod.* **2003**, *66*, 177−182.

(3) (a) Gutierrez, S.; Martinez-Lopez, D.; Moron, M.; Sucunza, D.; Sampedro, D.; Domingo, A.; Salgado, A.; Vaquero, J. J. *Chem.—Eur. J.* **2015**, *21*, 18758−18763. (b) Tsai, M.-S.; Ou, C.-L.; Tsai, C.-J.; Huang, Y.-C.; Cheng, Y.-C.; Sun, S.-S.; Yang, J.-S. *J. Org. Chem.* **2017**, *82*, 8031−8039.

(4) (a) Ermoli, A.; Bargiotti, A.; Brasca, M. G.; Ciavolella, A.; Colombo, N.; Fachin, G.; Isacchi, A.; Menichincheri, M.; Molinari, A.; Montagnoli, A.; Pillan, A.; Rainoldi, S.; Sirtori, F. R.; Sola, F.; Thieffine, S.; Tibolla, M.; Valsasina, B.; Volpi, D.; Santocanale, C.; Vanotti, E. *J. Med. Chem.* **2009**, *52*, 4380−4390. (b) Chazeau, V.; Cussac, M.; Boucherle, A. *Eur. J. Med. Chem.* **1992**, *27*, 615−625. (c) Caldwell, J. P.; Bennett, C. E.; McCracken, T. M.; Mazzola, R. D.; Bara, T.; Buevich, A.; Burnett, D. A.; Chu, I.; Cohen-Williams, M.; Josein, H.; Hyde, L.; Lee, J.; McKittrick, B.; Song, L.; Terracina, G.; Voigt, J.; Zhang, L.; Zhu, Z. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5380−5384. (d) Tahtouh, T.; Elkins, J. M.; Filippakopoulos, P.; Soundararajan, M.; Burgy, G.; Durieu, E.; Cochet, C.; Schmid, R. S.; Lo, D. C.; Delhommel, F.; Oberholzer, A. E.; Pearl, L. H.; Carreaux, F.; Bazureau, J.-P.; Knapp, S.; Meijer, L. *J. Med. Chem.* **2012**, *55*, 9312−9330. (e) Xu, Y.; Brenning, B.; Clifford, A.; Vollmer, D.; Bearss, J.; Jones, C.; McCarthy, V.; Shi, C.; Wolfe, B.; Aavula, B.; Warner, S.; Bearss, D. J.; McCullar, M. V.; Schuch, R.; Pelzek, A.; Bhaskaran, S. S.; Stebbins, C. E.; Goldberg, A. R.; Fischetti, V. A.; Vankayalapati, H. *ACS Med. Chem. Lett.* **2013**, *4*, 1142−1147.

(5) For selected examples, see: (a) Selvaraju, M.; Sun, C.-M. *ACS Comb. Sci.* **2015**, *17*, 182−189. (b) Renault, S.; Bertrand, S.; Carreaux, F.; Bazureau, J. P. *J. Comb. Chem.* **2007**, *9*, 935−942. (c) Dražić, T.; Molčanov, K.; Jurin, M.; Roje, M. *Synth. Commun.* **2017**, *47*, 764−770. (d) Roué, N.; Bergman, J. *Tetrahedron* **1999**, *55*, 14729−14738. (e) Molina, P.; Tarraga, A.; Lidon, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1727−1731. (f) Muselli, M.; Baudequin, C.; Perrio, C.; Hoarau, C.; Bischoff, L. *Chem. - Eur. J.* **2016**, *22*, 5520−5524.

(6) (a) Boulton, A. J.; Katritzky, A. R.; Hamid, A. M. *J. Chem. Soc. C* **1967**, 2005−2007. (b) Afridi, A. S.; Katritzky, A. R.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 315−320.

(7) For a book: *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Amsterdam, 1996; Vols. *1*−*9*.

(8) For selected reviews and examples of rearrangement with isoxazoles, see: (a) Hu, F.; Szostak, M. *Adv. Synth. Catal.* **2015**, *357*, 2583−2614. (b) Jones, R. C. F.; Chatterley, A.; Marty, R.; Owton, W. M.; Elsegood, M. R. J. *Chem. Commun.* **2015**, *51*, 1112−1115. (c) Martorana, A.; Pace, A.; Buscemi, S.; Piccionello, A. P. *Org. Lett.* **2012**, *14*, 3240−3243. (d) Martorana, A.; Piccionello, A. P.; Buscemi, S.; Giorgi, G.; Pace, A. *Org. Biomol. Chem.* **2011**, *9*, 491−496. (e) Pace, A.; Pierro, P.; Buscemi, S.; Vivona, N.; Barone, G. *J. Org. Chem.* **2009**, *74*, 351−358.

(9) For selected examples of rearrangement with 1,2,4-oxadiazoles, see: (a) Knouse, K. W.; Ator, L. E.; Beausoleil, L. E.; Hauseman, Z. J.; Casaubon, R. L.; Ott, G. R. *Tetrahedron Lett.* **2017**, *58*, 202−205. (b) Palumbo Piccionello, A.; Guarcello, A.; Pace, A.; Buscemi, S. *Eur. J. Org. Chem.* **2013**, *2013*, 1986−1992. (c) Pace, A.; Pibiri, I.; Palumbo Piccionello, A.; Buscemi, S.; Vivona, N.; Barone, G. *J. Org. Chem.* **2007**, *72*, 7656−7666.

(10) For a mechanistic study, see: (a) Pace, A.; Pibiri, I.; Palumbo Piccionello, A.; Buscemi, S.; Vivona, N.; Barone, G. *J. Org. Chem.* **2007**, *72*, 7656−7666. (b) Frenna, V.; Palumbo Piccionello, A.; Cosimelli, B.; Ghelfi, F.; Spinelli, D. *Eur. J. Org. Chem.* **2014**, *2014*, 7006−7014. (c) D'Anna, F.; Frenna, V.; Macaluso, G.; Marullo, S.; Morganti, S.; Pace, V.; Spinelli, D.; Spisani, R.; Tavani, C. *J. Org. Chem.* **2006**, *71*, 5616−5624. (d) D'Anna, F.; Frenna, V.; Macaluso, G.; Morganti, S.; Nitti, P.; Pace, V.; Spinelli, D.; Spisani, R. *J. Org. Chem.* **2004**, *69*, 8718−8722. (e) Cosimelli, B.; Frenna, V.; Guernelli, S.; Lanza, C. Z.; Macaluso, G.; Petrillo, G.; Spinelli, D. *J. Org. Chem.* **2002**, *67*, 8010−8018.

(11) (a) Piccionello, A. P.; Buscemi, S.; Vivona, N.; Pace, A. *Org. Lett.* **2010**, *12*, 3491−3493. (b) Piccionello, A. P.; Pace, A.; Buscemi, S.; Vivona, N. *Org. Lett.* **2009**, *11*, 4018−4020. (c) Palumbo Piccionello, A.; Pace, A.; Buscemi, S.; Vivona, N.; Pani, M. *Tetrahedron* **2008**, *64*, 4004−4010. (d) Ruccia, M.; Vivona, N.; Cusmano, G. *Tetrahedron* **1974**, *30*, 3859−3864. (e) Ruccia, M.; Vivona, N.; Cusmano, G. *Tetrahedron Lett.* **1972**, *13*, 4959−4960.

(12) Qiu, F.; Liu, J.; Chen, S.; Li, N. *Adv. Synth. Catal.* **2019**, *361*, 481−484.

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Org. Lett. XXXX, XXX, XXX−XXX