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1,4-Palladium Shift/C(sp^3)−H Activation Strategy for the Remote Construction of Five-Membered Rings

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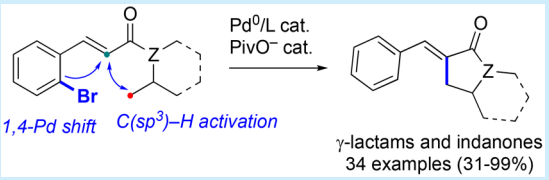
Supporting Information

ABSTRACT: 1,*n*-Metal shift is an elegant alternative approach enabling the functionalization of remote C−H bonds from simple precursors. In this work, we report a novel and simple Pd^0-catalyzed domino reaction involving 1,4-palladium shift and C(sp^3)−H activation and leading to (fused) five-membered rings. This method allowed access to a broad range of valuable arylidene γ-lactams and indanones and was applied to the formal synthesis of (−)-pyrrolam.



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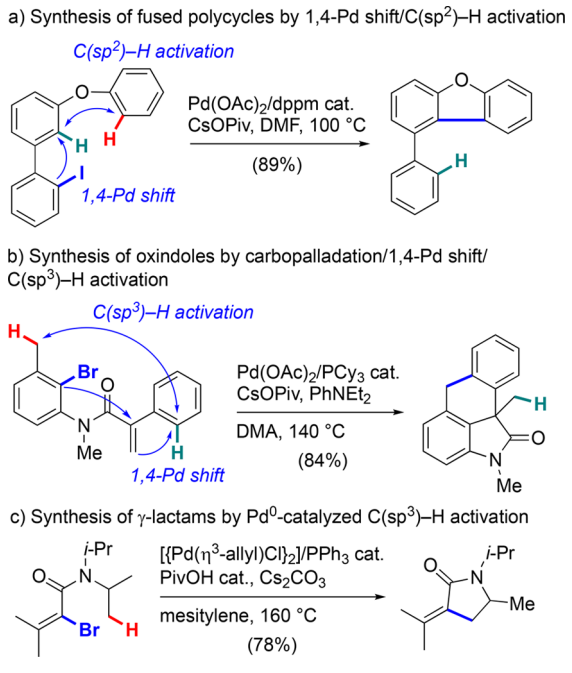
The last two decades witnessed impressive developments in the formation of carbon−carbon and carbon−heteroatom bonds by transition-metal-catalyzed C−H activation, generally affording improved atom- and step-economy compared to traditional cross-coupling methods.[1] In addition to direct C−H functionalization methods, strategies based on 1,*n*-metal shift allow the functionalization of distal C−H bonds which may be otherwise difficult to access.[2] Since the initial observation of 1,4-palladium shift by Heck in 1972,[3] a number of 1,*n*-Pd migrations occurring between a wide range of C(sp^2)- or C(sp^3)-hybridized carbon atoms have been reported.[2] In 2003, Larock and co-workers showed the first example of Pd^0-catalyzed domino reaction[4] involving oxidative addition, 1,4-Pd shift, and C(sp^2)−H arylation, resulting in the construction of complex polycyclic molecules (Scheme 1a).[5] Later, they reported a domino reaction involving 1,4-Pd shift, carbopalladation, and C(sp^3)−H activation to form a fused cyclopropane.[6] A few years later, Zhu and co-workers described a general method to access fused oxindoles by combining carbopalladation, 1,4-Pd shift, and activation of benzylic C(sp^3)−H bonds (Scheme 1b).[7] However, to the best of our knowledge, there is no example of a method simply combining oxidative addition, 1,4-Pd shift, and C(sp^3)−H activation without an intermediate carbopalladation step. In the past years, our group has developed a set of Pd^0-catalyzed methods for the direct functionalization of C(sp^3)−H bonds from precursors containing a C(sp^2)−X bond (X = leaving group).[8] In particular, we reported the synthesis of (fused) γ-lactams from alkenyl bromides (Scheme 1c).[9] To extend the scope of this reaction, we hypothesized that the organopalladium intermediate arising from C−Br oxidative addition might be also generated by 1,4-Pd shift from a more remote C−X bond. Such an indirect strategy would allow the use of less congested, easily accessible substrates.

A mechanistic blueprint for this domino process is depicted in Scheme 2. Oxidative addition from aryl bromide **1** followed by bromide−carboxylate exchange leads to organopalladium intermediate **A**. Subsequent C(sp^2)−H activation through the carboxylate-mediated concerted metalation−deprotonation

Scheme 1. 1,4-Pd Shift/C−H Activation and Synthesis of γ-Lactams



mechanism[10] affords the 5-membered palladacycle **B**. The latter is too strained to undergo reductive elimination and should readily open by proton transfer from the coordinated carboxylic acid, according to previous experimental observations[11] and mechanistic studies,[12] to give intermediate **C**. These two steps from **A** to **C** result in the net aryl to vinyl 1,4-Pd shift.[13,14] Organopalladium **C** is the same intermediate formed during the previous direct C(sp^3)−H activation reaction (see Scheme 1c).[9] Hence, base-mediated C(sp^3)−H activation from

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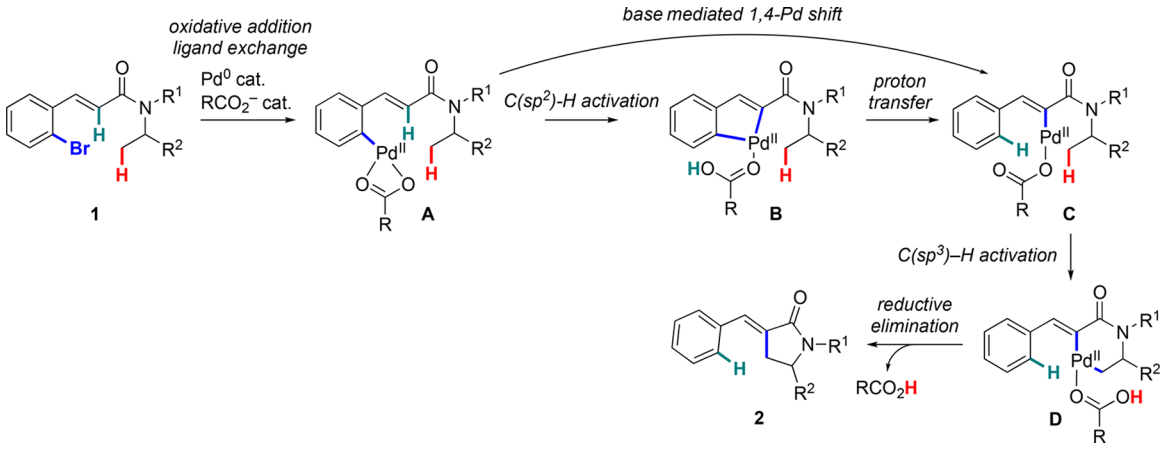
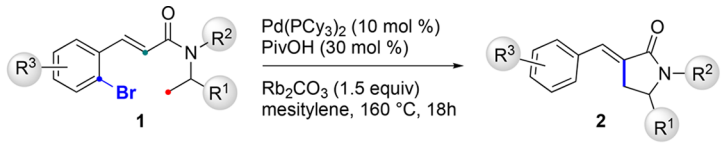
Scheme 2. Mechanistic Hypothesis[a]

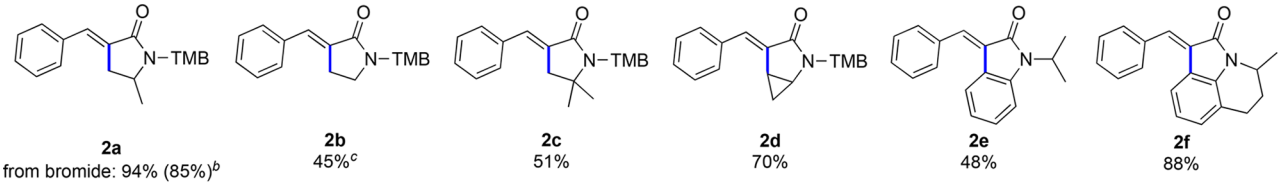


[a]The ligand has been omitted for clarity.

Scheme 3. Scope of the Synthesis of α-Arylidene γ-Lactams[a]

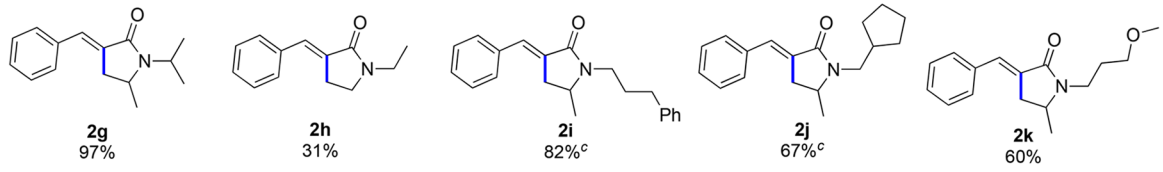


a) Variation of R^1

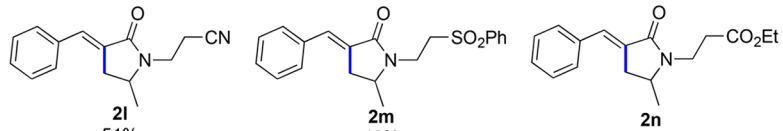


2a from bromide: 94% (85%)[b] from chloride: 55%; **2b** 45%[c]; **2c** 51%; **2d** 70%; **2e** 48%; **2f** 88%

b) Variation of R^2

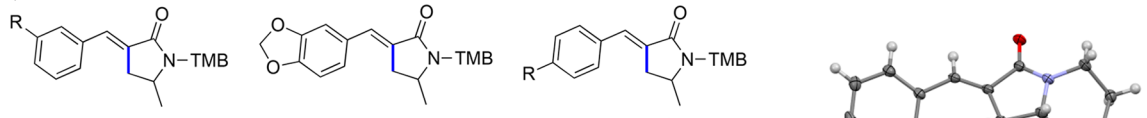


2g 97%; **2h** 31%; **2i** 82%[c]; **2j** 67%[c]; **2k** 60%



2l 51%; **2m** 40%; **2n** 62%

c) Variation of R^3



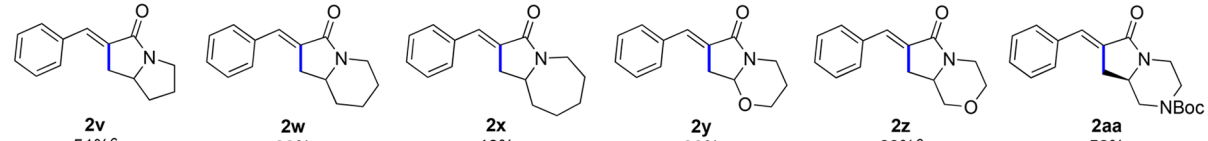
2o: R = F, 51%
2p: R = CF_3, 77%
2q: R = OMe, quant.
2r: R = OBn, 73%

2s 71%

2t: R = F, 64%
2u: R = Me, 76%[c]

Xray structure of **2y**[d]

d) Bicyclic products



2v 51%[c]; **2w** 98%; **2x** 40%; **2y** 90%; **2z** 69%[c]; **2aa** 52%

[a]All reactions were performed on a 0.1 mmol scale unless otherwise noted. [b]Performed on a 1 mmol scale. [c]Using additional PCy_3 (10 mol %). [d]Thermal ellipsoids shown at 50% probability. TMB = 2,4,6-trimethoxybenzyl.

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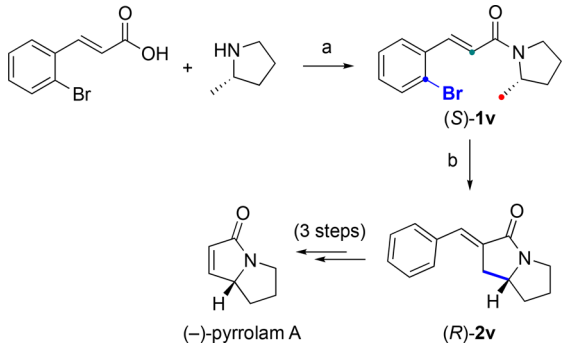
C and reductive elimination from the resulting 6-membered palladacycle **D** would lead to γ-lactam **2**. At this point, we were aware of potential pitfalls resulting from the lack of precedence for (1) 1,4-Pd shift onto the α-position of an α,β-unsaturated system and (2) the combination of 1,4-Pd shift with the activation of nonactivated C(sp^3)−H bonds. Herein, we report the development of such a domino reaction to access a wide range of arylidene γ-lactams and indanones.

We started our investigations with the synthesis of γ-lactams **2** (Scheme 3). The optimization of reaction conditions was performed on the TMB-protected[15] isopropylamide **1a** derived from 2-bromocinnamic acid (Table S1). The desired product **2a** was obtained in 94% yield on a 0.1 mmol scale using the well-defined complex $Pd(PCy_3)_2$ as the catalyst,[16] co-catalytic pivalic acid, and Rb_2CO_3 as the stoichiometric base in mesitylene at 160 °C. This high temperature was required, similar to our previous study on the direct reaction,[9] to favor the formation of the strained α-arylidene γ-lactam and avoid the protodebromination side reaction. The reaction also proceeded satisfyingly on a 10-fold (1 mmol) scale, giving rise to **2a** in 85% yield. With the optimized conditions in hand, we studied the scope of the reaction. Addition of free PCy_3 (10 mol %) was found to be beneficial in some cases, presumably to avoid catalyst decomposition. Using the aryl chloride instead of the bromide also furnished **2a**, albeit in lower yield (55%). The influence of the alkyl group undergoing C−H activation was first studied on amides containing the TMB group (Scheme 3a). Average to good yields were achieved for ethyl (**2b**), *tert*-butyl (**2c**), as well as cyclopropyl (**2d**) groups. The former is a challenging case due to the lesser number of methyl groups and the lack of a Thorpe−Ingold effect favoring the C(sp^3)−H activation step. Expectedly, the competition between C(sp^2)−H and C(sp^3)−H activation was clearly in favor of the former, giving rise to the interesting (fused) oxindoles **2e**,**f**. Substrates bearing two potentially reactive substituents on the amide nitrogen were next examined (Scheme 3b). Average to very good yields were observed, together with a high site-selectivity for the primary positions of the isopropyl group vs equidistant secondary positions (**2i**, **2k**−**n**), including much more acidic ones adjacent to nitrile, sulfone, and ester groups (**2l**−**n**). It should be noted that the β-lactam arising from C−H activation at the α-position to the nitrogen atom[9,17] was never observed (e.g., **2b**, **2d**, **2h**). Next, the effect of substituents on the aromatic ring was studied (Scheme 3c). Electron-withdrawing or -donating groups at the *meta*- or *para*-position to the bromine atom were well tolerated, furnishing the corresponding products with good to excellent yields (**2o**−**u**). Interestingly, such α-arylidene γ-lactams have been shown to exhibit antifungal activities toward *Colletotrichum orbiculare*.[18] Finally, we turned our attention to the synthesis of bicyclic γ-lactams (Scheme 3d). The fused pyrrolidine **2v** and azepane **2x**, relevant to the synthesis of pyrrolizidine[19a] and *Stemona* alkaloids,[19b] respectively, were obtained from easily available precursors in 40−51% yield. In contrast, the fused piperidine **2w** was obtained in much higher yield (98%). This result was successfully extended to bicyclic 5,6-fused γ-lactams containing heteroatoms, such as oxazinanes **2y**−**z** and the enantiopure *N*-Boc-protected piperazine **2aa**. Of note, olefin isomerization of the reaction products was never observed.

Its application to the short formal synthesis of (−)-pyrrolam A, a pyrrolizidine alkaloid isolated from *Streptomyces olivaceus* strains,[20] illustrates the simplicity of the current method

Scheme 4. Formal Synthesis of (−)-Pyrrolam A[a]

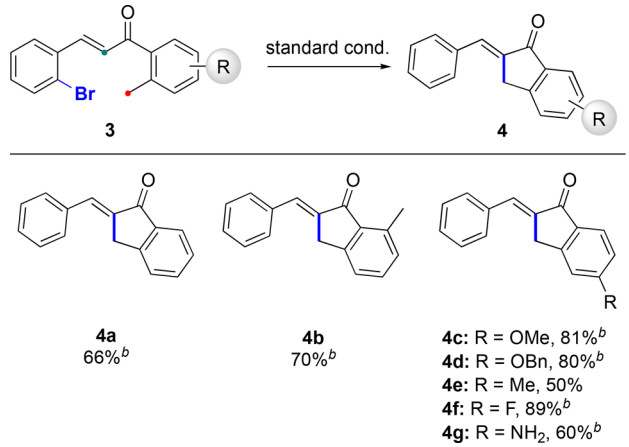


[a]Reaction conditions: (a) $(COCl)_2$ (1.5 equiv), Et_3N (2 equiv), CH_2Cl_2, 20 °C, quant; (b) $Pd(PCy_3)_2$ (10 mol %), PCy_3 (10 mol %), PivOH (30 mol %), Rb_2CO_3 (1.5 equiv), mesitylene (c = 0.025M), 160 °C, 18 h, 50%.

(Scheme 4). Standard amide formation from (*S*)-2-methylpyrrolidine and 2-bromocinnamic acid, both commercially available, gave the precursor for the key 1,4-Pd shift/C(sp^3)−H activation reaction (**1v**). The latter was reacted under standard conditions to afford the enantiopure γ-lactam **2v** in 50% yield. Compound **2v** was previously converted to (−)-pyrrolam A in three steps;[21] hence, the current approach allows for the synthesis of pyrrolam A in only five steps.

Next, we turned our attention toward the extension of the current method to other α,β-unsaturated carbonyl substrates for which the direct C(sp^3)−H activation reaction is not known. In particular, we examined the reactivity of readily available chalcones **3** containing benzylic C(sp^3)−H bonds (Scheme 5).[22] The reaction proceeded remarkably well under

Scheme 5. Synthesis of Arylidene Indanones[a]



[a]Reaction conditions: see Scheme 3. [b]Using additional PCy_3 (10 mol %).

the standard conditions, thereby furnishing a range of arylidene indanones **4**. The reaction was compatible with electron-rich and electron-deficient substituents (**4b**−**f**), and even with a free aniline (**4g**), giving rise to the corresponding products in average to excellent yields (50−89%).[23] Of note, such compounds possess a variety of interesting biological properties.[24]

To gain mechanistic insights, we performed experiments with fully and partially deuterated substrate **1a**, bearing deuterium atoms on the key C(sp^2) and C(sp^3) positions undergoing C−H activation (Scheme S1). We observed an

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unexpectedly strong intermolecular D−H exchange,[12b] preventing us from analyzing the 1,4-Pd shift, but indicating that the C(sp^3)−H activation step (Scheme 2, **C** → **D**) is reversible and faster than the final reductive elimination leading to the strained α-arylidene γ-lactam ring.[9,16c]

In conclusion, we reported a simple, step-economical method to construct (fused) five-membered rings through a novel Pd^0-catalyzed domino reaction involving 1,4-palladium shift and C(sp^3)−H activation. The generality of this method was demonstrated on a broad range of arylidene γ-lactams and indanones, and its applicability was illustrated through the formal synthesis of (−)-pyrrolam. This work opens the way to the development of C(sp^3)−H functionalization reactions that are difficult to achieve through direct methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00187.

Supplementary tables and figures; procedural and spectral data (PDF)

Accession Codes

CCDC 1884100 contains 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) *Catalytic Transformations via C−H Activation*; Yu, J.-Q., Ed.; Science of Synthesis; Georg Thieme Verlag KG, Stuttgart, 2015; Vols. *1 and 2*. (b) Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 2.

(2) (a) Ma, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 7512. (b) Shi, F.; Larock, R. *Top. Curr. Chem.* **2009**, *292*, 123.

(3) Heck, R. F. *J. Organomet. Chem.* **1972**, *37*, 389.

(4) Tsui, G. C.; Lautens, M. In *Domino Reactions: Concepts for Efficient Organic Synthesis*; Tietze, L. F., Ed.; Wiley-VCH: Weinheim, 2014; pp 67−103.

(5) (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. For other examples see: (b) Tian, Q.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3329. (c) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372. (d) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (e) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340. (f) Shintani, R.; Otomo, H.; Ota, K.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 7305. (g) Wang, M.; Zhang, X.; Zhuang, Y.-X.; Xu, Y.-H.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 1341.

(6) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 7235.

(7) Piou, T.; Bunescu, A.; Wang, Q.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12385.

(8) Baudoin, O. *Acc. Chem. Res.* **2017**, *50*, 1114.

(9) Holstein, P.; Dailler, D.; Vantourout, J.; Shaya, J.; Millet, A.; Baudoin, O. *Angew. Chem., Int. Ed.* **2016**, *55*, 2805.

(10) (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(11) (a) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(12) (a) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (b) Kefalidis, C. E.; Davi, M.; Holstein, P. M.; Clot, E.; Baudoin, O. *J. Org. Chem.* **2014**, *79*, 11903.

(13) Hu, T.-J.; Zhang, G.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2897.

(14) The 1,4-Pd shift was initially proposed to occur through other types of mechanisms including oxidative addition/reductive elimination and concerted H transfer:[2b] (a) Singh, A.; Sharp, P. R. *J. Am. Chem. Soc.* **2006**, *128*, 5998. (b) Mota, A. J.; Dedieu, A.; Bour, C.; Suffert, J. *J. Am. Chem. Soc.* **2005**, *127*, 7171. (c) Mota, A. J.; Dedieu, A. *J. Org. Chem.* **2007**, *72*, 9669.

(15) Pedroni, J.; Cramer, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 11826.

(16) (a) Guyonnet, M.; Baudoin, O. *Org. Lett.* **2012**, *14*, 398. (b) Rocaboy, R.; Dailler, D.; Baudoin, O. *Org. Lett.* **2018**, *20*, 772. (c) Rocaboy, R.; Dailler, D.; Zellweger, F.; Neuburger, M.; Salomé, C.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2018**, *57*, 12131.

(17) Dailler, D.; Rocaboy, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2017**, *56*, 7218.

(18) Delong, W.; Lanying, W.; Yongling, W.; Shuang, S.; Juntao, F.; Xing, Z. *Eur. J. Med. Chem.* **2017**, *130*, 286.

(19) (a) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721. (b) Pilli, R. A.; Rosso, G. B.; de Oliveira, M. C. F. *Nat. Prod. Rep.* **2010**, *27*, 1908.

(20) Grote, R.; Zeeck, A.; Stümpfel, J.; Zähner, H. *Liebigs Ann. Chem.* **1990**, *1990*, 525.

(21) Aoyagi, Y.; Manabe, T.; Ohta, A.; Kurihara, T.; Pang, G.-L.; Yuhara, T. *Tetrahedron* **1996**, *52*, 869.

(22) Nonaromatic α,β-unsaturated ketone reactants failed to give the corresponding arylidene pentanones.

(23) Park, S.; Kadayat, T. M.; Jun, K.-Y.; Magar, T. B. T.; Bist, G.; Shrestha, A.; Lee, E. S.; Kwon, Y. *Eur. J. Med. Chem.* **2017**, *125*, 14.

(24) Menezes, J. C. J. M. D. S. *RSC Adv.* **2017**, *7*, 9357.

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Org. Lett. XXXX, XXX, XXX−XXX