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Lewis Acid-Catalyzed Formal [3+3] Annulation of Propargylic Alcohols with 4-Hydroxy-2*H*-chromen-2-ones

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Abstract. A Lewis acid-catalyzed formal [3+3] cascade annulation strategy for the formation of diverse tricyclic compounds possessing functionalized pyrano[3,2-c]chromen-5(2*H*)-one fragments has been developed using propargylic alcohols and 4-hydroxy-2*H*-chromen-2-ones as the substrates. The protocol provides a one-step, environmentally benign method of accessing a broad range of pyrano[3,2-c]chromen-5(2*H*)-one derivatives in excellent yields under mild conditions and with good functional-group tolerance. The method is effective on the gram scale, which highlights the inherent practicality of this synthetic transformation.

Keywords: 4-hydroxy-2*H*-chromen-2-ones; nucleophilic addition; Lewis acids; alcohols; pyrano[3,2-c]chromen-5(2*H*)-one derivatives

The pyrano[3,2-c]chromen-5(2*H*)-one derivatives represent one of the most important classes of oxygen-containing compounds because they are embedded in a wide array of biologically active natural products, pharmaceutically relevant molecules, agrochemicals, and key skeletal structures in organic chemistry and materials science.[1] For example, the biologically active prenylated coumarin ferprenin, isolated from *Ferulu communis*, was identified as having the ability to cause severe hemorrhagic disease (Figure 1).[2] Arisugacin A, which was isolated from the culture broth of *Penicillium sp. Fo-4259*, is the most selective and potent known inhibitor against serum butyrylcholinesterase and erythrocytes acetylcholinesterase, and thus, it has therapeutic significance for the treatment of dementia.[3] Pyripyropene A, isolated from a fermentation broth of *Aspergillus fumigatus* FO-1289 by the Omura group, showed potent inhibitory activities against acyl-CoA and cholesterol acyltransferase and has potential for the prevention and treatment of atherosclerosis.[4] (+)-Calanolide A, a dipyranocoumarin isolated by Boyd and co-workers from the rainforest tree *Calophyllum lanigerum* var, is a member of a subclass of HIV-1-specific reverse transcriptase inhibitors.[5] Due to the importance and ubiquity of this framework in organic chemistry, the development of new reliable approaches for the synthesis of pyrano[3,2-c]chromen-5(2*H*)-one derivatives has attracted considerable attention. In 2011, Wang et al. reported a palladium-catalyzed cascade transformation of coumarins and alkynes for the construction of highly substituted cyclopentadiene-fused chromones (Scheme 1a).[6] An unusual secondary amine-thiourea promoted reaction for the synthesis of barbiturate-fused tetrahydropyrano derivatives employing 4 hydroxycoumarins and nitroalkenes as the substrates has been disclosed by the Chen group (Scheme 1b).[7] Xu and co-workers developed an efficient synthesis of valuable pyranocoumarins through a gold (III) catalyzed tandem annulation of 4-hydroxycoumarins and α,β-unsaturated ketones. (Scheme 1c).[8] Despite several methods having been reported,[9] there is still demand for new methodologies that are more efficient and environmentally benign for the generation of pyrano[3,2-c]chromen-5(2*H*)-one derivatives.

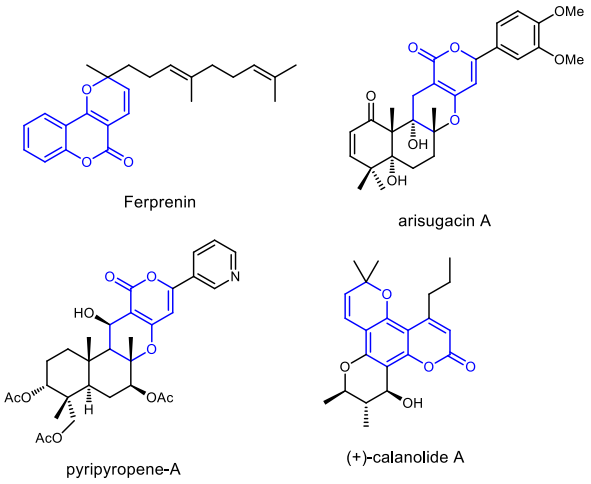

Figure 1. Select biologically active natural compounds that contain this structural motif

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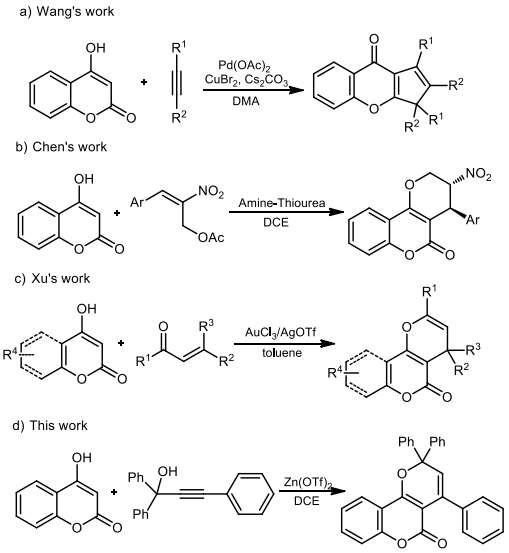
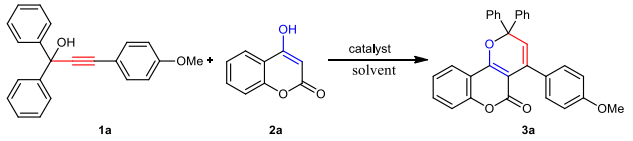
During the past decade, the rapid development of Lewis acid-catalyzed cascade annulations has afforded practical, versatile, and atom-economical methods of accessing complex heterocycles, carbocycles and condensed ring scaffolds that are not easily synthesized by traditional methods. In particular, Lewis acid-catalyzed annulations of propargylic alcohols with a broad range of nucleophiles and electrophiles have enabled the efficient construction of pyrroles,[10] furans,[11] indoles,[12] pyridines,[13] quinoline,[14] thiazoles,[15] and azepines.[16] Inspired by these intriguing discoveries for propargylic alcohols, we herein describe the development of a zinc-catalyzed formal [3+3] cascade annulation of propargylic alcohols with 4-hydroxy-2*H*-chromen-2-ones, leading to the facile formation of pyrano[3,2-c]chromen-5(2*H*)-one derivatives in excellent yields under mild conditions.

Scheme 1. Summary of present studies and our proposed methods of accessing tricyclic compounds



We began this investigation by exploring the reaction between propargylic alcohol (**1a**) and 4-hydroxy-2*H*-chromen-2-one (**2a**) using several different combinations of Lewis acid catalysts, temperature, reaction time, and solvents. To our delight, desired product **3a** was obtained in a moderate yield of 55% in the presence of a catalytic amount of $Y(OTf)_3$ (10 mol %) in THF at 80 °C in 4 h in high pressure seal tube (Table 1, entry 1). The structure of product **3a** was unambiguously determined by NMR spectroscopy and X-ray crystallography (see the Supporting Information).[17] Among the different Lewis acid catalysts screened, $Zn(OTf)_2$ exhibited the best catalytic activity and gave the desired product in 65% yield (entries 2−6). Subsequent investigation of the reaction conditions revealed that 100 °C was optimal for the formal [3+3] annulation reaction, as it furnished the expected product in 71% yield (entries 7−9). Moreover, it was found that the yield improved slightly (to 75%) when

Table 1. Optimization of the conditions of the reaction of **1a** with 4-hydroxy-2*H*-chromen-2-one [a, b]



entry	catalyst (10 mol %)	solvent	temp (°C)	*t* (h)	yield (%)[b]
1	$Y(OTf)_3$	THF	80	4	55
2	$Yb(OTf)_3$	THF	80	4	59
3	$Al(OTf)_3$	THF	80	4	19
4	$Cu(OTf)_2$	THF	80	4	22
5	$Bi(OTf)_3$	THF	80	4	42
6	$Zn(OTf)_2$	THF	80	4	65
7	$Zn(OTf)_2$	THF	60	4	33
8	$Zn(OTf)_2$	THF	100	4	71
9	$Zn(OTf)_2$	THF	120	4	67
10	$Zn(OTf)_2$	THF	100	6	72
11	$Zn(OTf)_2$	THF	100	8	75
12	$Zn(OTf)_2$	THF	100	10	72
13	CH_3COOH	THF	100	8	29
14	TFA	THF	100	8	51
15	TsOH	THF	100	8	62
16	TfOH	THF	100	8	3
17	**$Zn(OTf)_2$**	**DCE**	**100**	**8**	**83**
18	$Zn(OTf)_2$	CH_3NO_2	100	8	49
19	$Zn(OTf)_2$	$PhCH_3$	100	8	61
20	$Zn(OTf)_2$	CH_3CN	100	8	77
21	$Zn(OTf)_2$	1,4-dioxane	100	24	53

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) and 4-hydroxy-2*H*-chromen-2-one **2a** (2.0 equiv.) in solvent (2.0 mL). [b] Yields are given for isolated products.

the reaction time was extended to 8 h (entries 10−12). Due to the reactions were conducted in high pressure seal tube, a lower temperature and short reaction time furnished expected product in lower yield. Notably, it was found that various Brønsted acid catalysts also performed well and afforded product **3a** in moderate to good yields, indicating that the formal [3+3] cascade annulation is proposed to proceed *via* a nucleophilic substitution pathway (entries 13−16). Further screening of solvents such as DCE, CH_3NO_2, $PhCH_3$, CH_3CN, and 1,4-dioxane led to a slightly higher yield (entries 17−21). Ultimately, the optimal reaction conditions for the construction of desired product **3a** were the use of alkynol **1a** (0.1 mmol), and 4-hydroxy-2*H*-chromen-2-one **2a** (2.0 equiv.) in the presence of $Zn(OTf)_2$ (10 mol %) in DCE (2.0 mL) at 100 °C for 8 h in high pressure seal tube.

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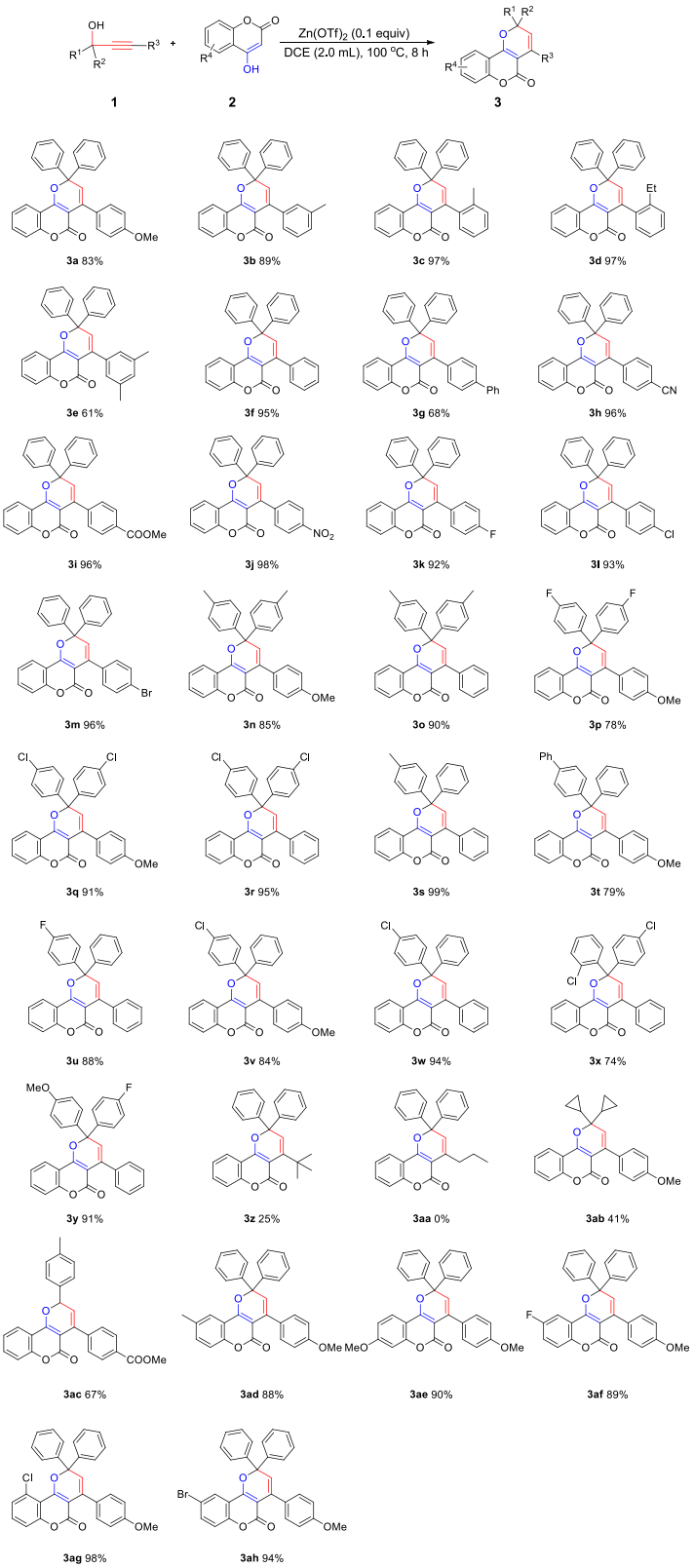
Scheme 2. Conversion of propargylic alcohols into pyrano[3,2-c]chromen-5(2*H*)-one derivatives [a, b]

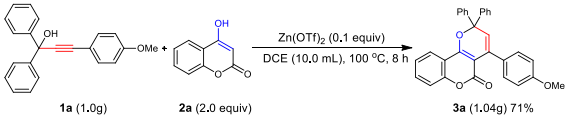


[a] Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **2** (2.0 equiv.) in the presence of $Zn(OTf)_2$ (10 mol %) in DCE (2.0 mL) at 100 °C for 8 h. [b] Yields are given for isolated products.

With the optimized reaction conditions established, we next investigated the generality of the scope of propargylic alcohols for the cascade annulation with **2**. As depicted in Scheme 2, the transformation of various substituted alkynol substrates with 4-hydroxy-2*H*-chromen-2-one proceeded smoothly and delivered the corresponding pyrano[3,2-c]chromen-5(2*H*)-one derivatives in moderate to excellent yields. A wide variety of functional groups, including methoxy, methyl, ethyl, 3,5-dimethyl, phenyl, cyano, ester, nitryl, and halogen substituents, were found to be compatible with the optimized reaction conditions. In general, aryl substituents with electron-donating properties (OMe, Me, Et, and 3,5-diMe; **3a**–**3e**) or electron-withdrawing properties (Ph, CN, COOMe, and NO_2; **3g**–**3j**), at any position on the phenyl ring (R^3), were well-tolerated and afforded the anticipated products in yields ranging from 61% to 98% (**3a**–**3j**). Various halogen substituents such as F, Cl, and Br on the aromatic ring (R^3) were compatible with the optimized conditions and generated the desired products **3k**–**3m** in 92–96% yields. Notably, these products have the potential for downstream chemical modifications. Several symmetrical propargylic alcohols bearing electron-rich (Me and OMe; **3n** and **3o**) or electron-deficient substituents (F and Cl; **3p**–**3r**) smoothly produced the corresponding products in 78–95% yields. Various unsymmetrical propargylic alcohols **1s**–**1y** were then investigated, and they were well-tolerated in this formal [3+3] cascade annulation and afforded the anticipated products **3s**–**3y** in good to excellent yields (74–99%). However, alkyl-substituted (R^3) propargylic alcohols (**1z** and **1aa**) gave moderate yields or even did not undergo the desired transformation. This outcome might be due to the fact that it is difficult for an alkyl group to stabilize active propargyl intermediate **A** generated by alkynol substrate **1** (see Scheme 4). The R^1 and R^2 substituents could also be cyclopropyl, and the corresponding product **3ab** was obtained in moderate yield. Remarkably, the transformation of secondary propargylic alcohol methyl 4-(3-hydroxy-3-(*p*-tolyl)prop-1-yn-1-yl)benzoate (**1ac**) proceeded smoothly and allowed the facile construction of corresponding product **3ac** in moderate yield. The 4-hydroxy-2*H*-chromen-2-ones bearing electron-donating (Me and OMe) or electron-withdrawing groups (F, Cl, and Br) on the aromatic ring (R^4) reacted smoothly and generated expected products **5ad**–**5ah** in 88–98% yields.

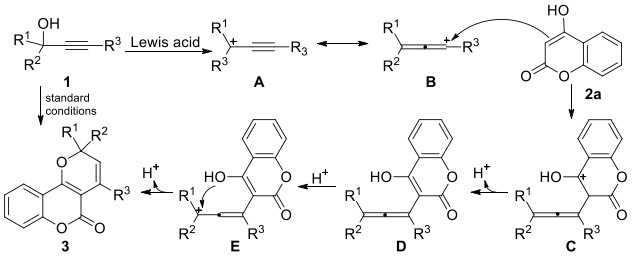
To evaluate the potential synthetic utility of this formal [3+3] cascade annulation, the reaction was carried out on a preparative scale under the standard reaction conditions, and desired product **3a** was isolated in 71% yield (Scheme 3).

Scheme 3. Large-scale experiment



A plausible mechanism based on the above experimental observations and published literature is illustrated in Scheme 4.[18,19] Initially, propargylic alcohol **1** is converted to active propargyl intermediate **A,** which could afford resonance-stabilized intermediate **B** by the presence of a Lewis acid catalyst ($Zn(OTf)_2$). Next, intermolecular nucleophilic attack of intermediate **B** by the double bond of 4-hydroxy-2*H*-chromen-2-one (**2a)** generates intermediate **C**, which could furnish intermediate **D** by the release of a proton. The protonation of intermediate **D** produces intermediate **E**, which could undergo intramolecular nucleophilic attack to afford desired product **3** and concomitant regeneration of the catalyst.

Scheme 4. Proposed mechanism for the formation of pyrano[3,2-c]chromen-5(2*H*)-one derivatives



In summary, we have developed a Lewis acid-catalyzed formal [3+3] cascade annulation of propargylic alcohols with 4-hydroxy-2*H*-chromen-2-ones that provides a practical, and environmentally benign method of assembling this tricyclic structural motif in excellent yields under mild conditions. Our developed reaction conditions tolerate a wide scope of typical organic functional groups. The highly efficient catalytic system, ambient reaction conditions, tricyclic structural products, operational simplicity, and good functional group compatibility of this strategy can be ranked among the most sustainable and convenient alternatives for the synthesis of pyrano[3,2-c]chromen-5(2*H*)-one derivatives.

Experimental Section

General procedure for the synthesis of compounds 3

The reactions of propargylic alcohols **1** (0.1 mmol), and substituted 4-hydroxy-2*H*-chromen-2-ones **2** (2.0 equiv), $Zn(OTf)_2$ (10 mol %) in DCE (2.0 mL) were conducted at 100 °C under an air atmosphere for 8.0 h. The reactions were completed by TLC monitoring. The resulting mixtures were cooled down to room temperature. The mixtures were evaporated under reduced pressure. The residues were further purified by chromatography on silica gel to afford the corresponding products **3**.

Acknowledgements

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References

[1] a) M. C. Ortiz Villamizar, F. I. Zubkov, C. E. Puerto Galvis, L. Y. Vargas Mendez, V. V. Kouznetsov, *Org. Chem. Front.* **2017**, *4*, 1736; b) E. J. Jung, B. H. Park, Y. R. Lee, *Green Chem*. **2010**, *12*, 2003; c) C.-C. Lin, C.-C. Hsieh, Y.-C. Yu, C.-H. Lai, C.-N. Huang, P.-Y. Kuo, C.-H. Lin, D.-Y. Yang, P.-T. Chou, *J. Phys. Chem. A*. **2009**, *113*, 9321; d) R.-Y. Yang, D. Kizer, H. Wu, E. Volckova, X.-S. Miao, S. M. Ali, M. Tandon, R. E. Savage, T. C. K. Chan, M. A. Ashwell, *Bioorg. Med. Chem*. **2008**, *16*, 5635; e) C. Hubert, J. Moreau, J. Batany, A. Duboc, J.-P. Hurvois, J.-L. Renaud, *Adv. Synth. Catal*. **2008**, *350*, 40; f) G. Appendino, G. Cravotto, G. B. Giovenzana, G. Palmisano, *J. Nat. Prod*. **1999**, *62*, 1627; g) R. J. Kumar, G. L. D. Krupadanam, G. Srimannarayana, *Synthesis* **1990**, 535.

[2] a) Q. Yang, L.-H. Zhou, W.-X. Wu, W. Zhang, N. Wang, X.-Q. Yu, *RSC Adv*. **2015**, *5*, 78927; b) G. Appendino, S. Tagliapietra, G. M. Nano, V. Picci, *Phytochemistry* **1988**, *27*, 944.

[3] a) J. Moreau, C. Hubert, J. Batany, L. Toupet, T. Roisnel, J.-P. Hurvois, J.-L. Renaud, *J. Org. Chem*. **2009**, *74*, 8963; b) F. Kuno, K. Otoguro, K. Shiomi, Y. Iwai, S. Omura. *J. Antibiot.* **1996**, *49*, 742; c) F. Kuno, K. Shiomi, K. Otoguro, T. Sunazuka, S. Omura. *J. Antibiot.* **1996**, *49*, 748.

[4] a) A. B. Smith, T. Kinsho, T. Sunazuka, S. Ōmura, *Tetrahedron Lett.* 1996, 37, 6461; b) T. Nagamitsu, T. Sunazuka, R. Obata, H. Tomoda, H. Tanaka, Y Harigaya, S. Omura, A. B. Smith, *J. Org. Chem*. **1995**, *60*, 8126.

[5] a) T. C. McKee, C. D. Covington, R. W. Fuller, H. R. Bokesch, S. Young, J. H. Cardellina, M. R. Kadushin, D. D. Soejarto, P. F. Stevens, G. M. Cragg, M. R. Boyd, *J. Nat. Prod*. **1998**, *61*, 1252; b) D. L. Galinis, R. W. Fuller, T. C. McKee, J. H. Cardellina, R. J. Gulakowski, J. B. McMahon, M. R. Boyd, *J. Med. Chem*.**1996**, *39*, 4507.

[6] L. Wang, S. Peng, J. Wang, *Chem. Commun*. **2011**, *47*, 5422.

[7] J. Zhang, G. Yin, Y. Du, Z. Yang, Y. Li, L. Chen, *J. Org. Chem.* **2017**, *82*, 13594.

[8] Y. Liu, J. Zhu, J. Qian, B. Jiang, Z. Xu, *J. Org. Chem.***2011**, *76*, 9096.

[9] a) Z. Zhou, H. Liu, Y. Li, J. Liu, Y. Li, J. Liu, J. Yao C. Wang, *ACS Comb. Sci*. **2013**, *15*, 363; b) M. R. Zanwar, M. J. Raihan, S. D. Gawande, V. Kavala, D. Janreddy, C.-W. Kuo, R. Ambre, C.-F. Yao, *J. Org. Chem*. **2012**, *77*, 6495.

[10] G. C. Nandi, S. K, *J. Org. Chem.* **2016**, *81*, 11909.

[11] a) X. Cheng, Y. Yu, Z. Mao, J. Chen, X. Huang, *Org. Biomol. Chem*. **2016**, 14, 3878; b) C. Qi, H. Jiang, L. Huang, G. Yuan, Y. Ren, *Org. Lett*. **2011**, *13*, 5520.

[12] a) C. Raji Reddy, R. Rani Valleti, P. Sathish, *J. Org. Chem.* **2017**, *82*, 2345; b) S. Muthusamy, A. Balasubramani, E. Suresh, *Adv. Synth. Catal*. **2017**,

359, 786; c) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett*. **2015**, *17*, 4372.

[13] a) G. Yin, Y. Zhu, N. Wang, P. Lu, Y. Wang, *Tetrahedron* **2013**, *69*, 8353; b) Y. Shao, K. Zhu, Z. Qin, E. Li, Y. Li, *J. Org. Chem.***2013**, *78*, 5731.

[14] G. Ranjith Kumar, R. Kumar, M. Rajesh, M. Sridhar Reddy, *Chem. Commun*. **2018**. DOI: 10.1039/c7cc08408k.

[15] X. Zhang, W. T. Teo, Sally, P. W. H. Chan, *J. Org. Chem.* 2010, 75, 6290.

[16] a) Y.-P. Han, X.-R. Song, Y.-F. Qiu, H.-R. Zhang, L.-H. Li, D.-P. Jin, X.-Q. Sun, X.-Y. Liu, Y.-M. Liang, *Org. Lett*. **2016**, *18*, 940; b) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti, *Org. Lett*. **2016**, *18*, 3511.

[17] CCDC 1814500 {4-(4-methoxyphenyl)-2,2-diphenylpyrano[3,2-c]chromen-5(2*H*)-one **3a**} contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] a) X. Yin, H. Mohammad, H. E. Eldesouky, A. Abdelkhalek, M. N. Seleem, M. Dai, *Chem. Commun*. **2017**, *53*, 7238; b) M. Sen, P. Dahiya, J. R. Premkumar, B. Sundararaju, *Org. Lett*. **2017**, *19*, 3699; c) X.-F. Mao, X.-P. Zhu, D.-Y. Li, L.-L. Jiang, P.-N. Liu, *Chem. Commun*. **2017**, *53*, 8608; d) G. Hu, C. Shan, W. Chen, P. Xu, Y. Gao, Y. Zhao, *Org. Lett*. **2016**, *18*, 6066; e) L. Hao, F. Wu, Z.-C. Ding, S.-X. Xu, Y.-L. Ma, L. Chen, Z.-P. Zhan, *Chem. Eur. J*. **2012**, *18*, 6453.

[19] a) M. Nogami, K. Hirano, M. Kanai, C. Wang, T. Saito, K. Miyamoto, A. Muranaka, M. Uchiyama, *J. Am. Chem. Soc*. **2017**, *139*, 12358; b) P. Tharra, B. Baire, *Chem. Commun*. **2016**, *52*, 12147; c) S. Wang, Y. Zhu, Y. Wang, P. Lu, *Org. Lett*. **2009**, *11*, 2615.

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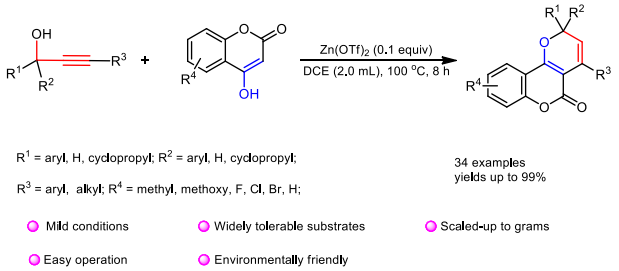

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