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Visible-light induced metal-free cascade Wittig/hydroalkylation reactions†

Pannan Miao,[a] Ruining Li,[a] Xianfeng Lin,[a] Liangming Rao[b,c] and Zhankui Sun *[a,b]

Cascade reactions are green and powerful transformations for building multiple carbon–carbon bonds in one step. Through a relay olefination and radical addition process, we were able to develop the cascade Wittig/hydroalkylation reactions induced by visible light. This metal-free radical approach features mild conditions, robustness, and excellent functionality compatibility. It allows access to saturated C3 homologation products directly from aldehydes or ketones. The synthetic utility of this method is demonstrated by a two-step synthesis of indolizidine 209D.

Introduction

Cascade reactions are powerful, efficient and elegant processes for building complex molecules through two or more consecutive steps in a single operation.[1] They are appealing because of obvious benefits, such as atom economy, as well as economies of time, labor, waste generation, *etc.*[2] The design and implementation of cascade reactions is a challenging yet interesting process, and radicals are often involved.[3] Herein, we disclose novel metal-free radical cascade Wittig/hydroalkylation reactions induced by visible light.

The Wittig reaction allows the preparation of an alkene by the reaction of an aldehyde or ketone with a phosphonium ylide, typically with triphenylphosphine oxide as the byproduct.[4] If the following reaction could tolerate triphenylphosphine oxide and use the alkene as the substrate, then a cascade reaction would be possible. Based on the studies by our group and other groups,[5] we designed a cascade reaction as shown in Fig. 1b. We propose to generate radical intermediate **I** through the desulfurization procedure from thiol, with triphenylphosphine sulfide as the byproduct (Fig. 1c). This electrophilic radical **I** would add to the electron-rich alkene **II** which is formed through the Wittig reaction, and generate intermediate **III** which would deliver the final product through a hydrogen atom transfer process.[6] As the Wittig reaction and the radical generation step share similar byproducts and the following hydroalkylation process matches the polarity request for radical reactions, we believe that this cascade reaction is highly possible. By employing this cascade process, we could obtain the saturated C3 homologation product (**4**) directly from the aldehyde (**1**) in a single step, while there is only one particular method reported by Prof. Li to complete this transformation in one step (Fig. 1a).[7] In Li *et al.*'s work, they used

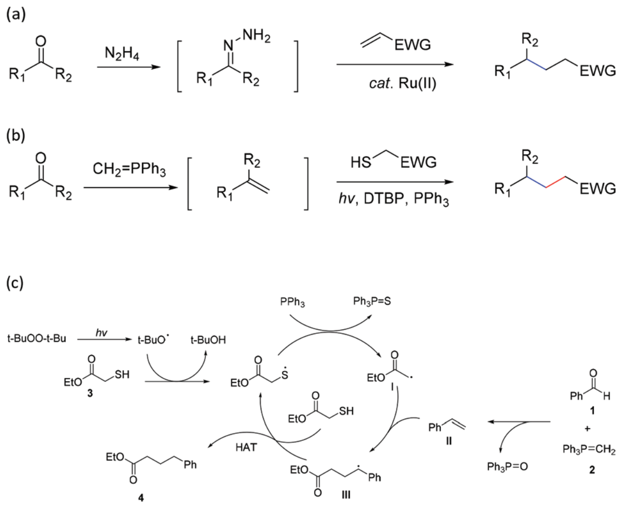

Fig. 1 (a) Carbonyl compounds as latent alkyl carbanions for conjugate additions. (b) This study: Visible-light induced cascade Wittig/hydroalkylation reaction. (c) Proposed mechanism for the cascade Wittig/hydroalkylation reaction. cat. = catalytic, EWG = electron-withdrawing group. HAT = hydrogen atom transfer.

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[a] *Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, Pharma-X Center, School of Pharmacy, Shanghai Jiao Tong University, No. 800 Dongchuan Rd., Shanghai 200240, China. E-mail: zksun@sjtu.edu.cn*

[b] *Huzhou Research and Industrialization Center for Technology, Chinese Academy of Sciences, 1366 Hongfeng Road, Huzhou 313000, China*

[c] *Shanghai Institute of nutrition and health, Chinese academy of sciences, 320 Yueyang Road, Shanghai, 200031, China*

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carbonyl compounds as latent alkyl carbanions and employed Ru(II) to catalyze the conjugate additions to electron-deficient alkenes. As such, a proposed mechanism for this Wittig/hydroalkylation reaction is shown in Fig. 1c.

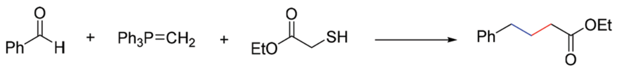
Results and discussion

We began our study by using benzaldehyde (**1**), ylide (**2**), and ethyl 2-mercaptoacetate (**3**) as model substrates and examined different conditions under visible light at room temperature. As expected, when the reaction was performed in DMSO, the desired product was isolated. But the yield was only 32% even with 3 equivalents of 2-mercaptoacetate (Table 1, entry 1). However, with DCM as the co-solvent, the yield was dramatically increased to 93% (Table 1, entry 2). The high yield was maintained when 2 equivalents of 2-mercaptoacetate were used (Table 1, entry 3). With less 2-mercaptoacetate, the yield was decreased to 88% (Table 1, entry 4). The reaction didn't proceed to deliver the desired product without DTBP or visible-light irradiation.

Having established the optimized conditions, we began to examine the scope of this transformation. We first checked different aromatic aldehydes. A diverse range of electron-donating (Ph, OMe and SMe) and electron-withdrawing functional groups (Cl, Br, I and CF_3) were entirely compatible and delivered the products in good to excellent yields (Table 2, substrates **5–9**, **11–15**). Even a free hydroxy group and a boronic acid group could be tolerated, albeit with lower yields (Table 2, substrates **10** and **16**). However, a boronic ester group provided a better yield (Table 2, substrate **17**). Other aromatic aldehydes such as nicotinaldehyde, thiazole aldehyde and thiophene aldehyde also reacted efficiently (Table 2, substrates **18–20**).

We next turned our attention to aliphatic aldehydes. 3-Phenylpropanal and 3-(furan-2-yl)propanal worked smoothly and provided the products in moderate yields (Table 3, substrates **21–23**). *N*-Cbz-piperidine aldehyde could also work (Table 3, substrate **24**). Different linear aliphatic aldehydes reacted efficiently to give the products in moderate to good yields (Table 3, substrates **25–30**). Notable examples included the ones bearing a hydroxy group (Table 3, substrate **26**) and a chloride group (Table 3, substrate **27**). As for substrate **28**

Table 1 Optimization of reaction conditions[a]

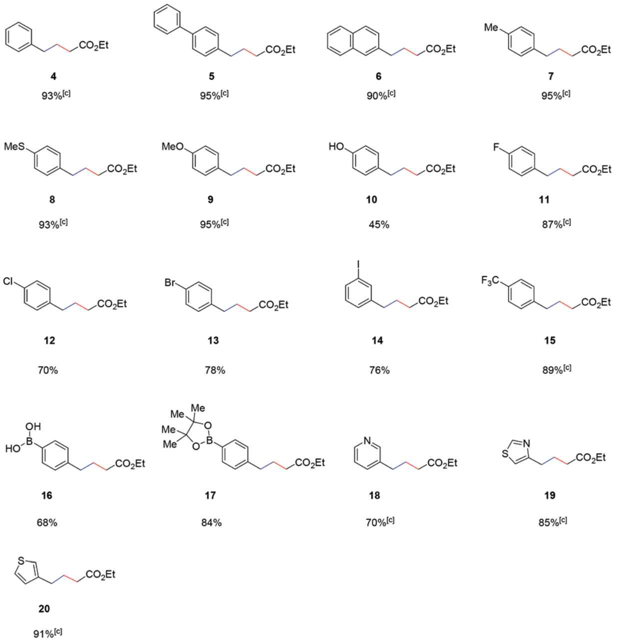


1 **2** **3** **4**

Entry	Substrate **3**	DTBP	PPh_3	Yields[b]
1	3.0 equiv.	6.0 equiv.	4.5 equiv.	32%[c]
2	3.0 equiv.	6.0 equiv.	4.5 equiv.	93%
3	**2.0 equiv.**	**4.0 equiv.**	**2.5 equiv.**	**93%**
4	1.5 equiv.	3.0 equiv.	1.9 equiv.	88%
5	2.0 equiv.		2.5 equiv.	N.D.
6	2.0 equiv.	4.0 equiv.	2.5 equiv.	N.D.[d]

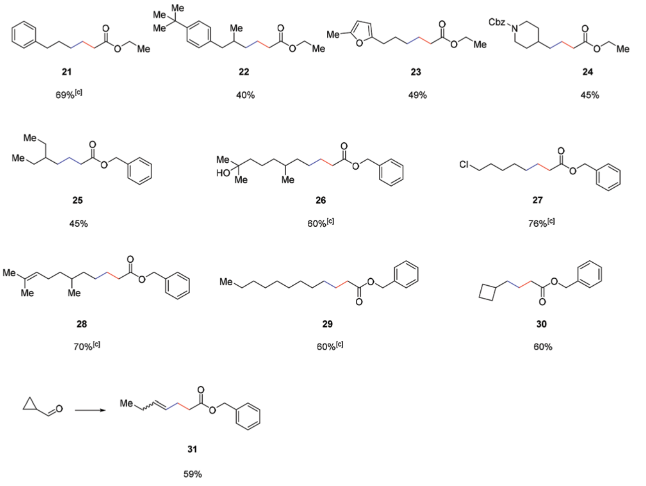
[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), 2-mercaptoacetate, DTBP, PPh_3, DMSO–DCM (4 mL : 4 mL), room temperature, 55 W household CFL bulb irradiation on two sides, 12 h. [b] Yields were determined by ^{1}H-NMR. N.D. = not detected. DTBP = di-*tert*-butyl peroxide. [c] DMSO was used as the solvent. [d] Without light.

Table 2 Substrate scope for the cascade reaction[a,b]



[a] Reaction conditions: Aldehyde (1.0 mmol), ylide (1.2 mmol), 2-mercaptoacetate (2.0 mmol), DTBP (4.0 mmol), PPh_3 (2.5 mmol), DMSO–DCM (4 mL : 4 mL), room temperature, 55 W household CFL bulb irradiation on two sides, 12 h. [b] Isolated yields. [c] Yields were determined by ^{1}H-NMR.

Table 3 Substrate scope for the cascade reaction[a,b]



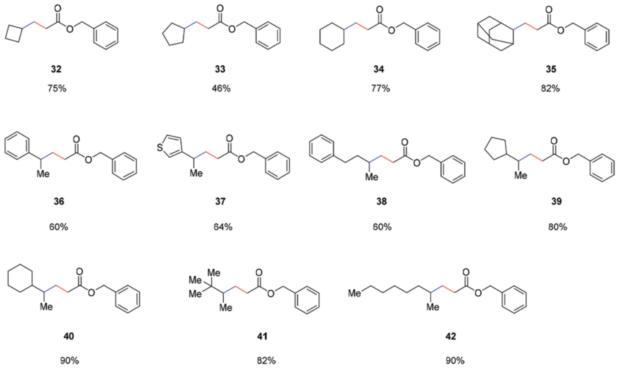
[a] Reaction conditions: Aldehyde (1.0 mmol), ylide (1.2 mmol), 2-mercaptoacetate (2.0 mmol), DTBP (4.0 mmol), PPh_3 (2.5 mmol), DMSO–DCM (4 mL : 4 mL), room temperature, 55 W household CFL bulb irradiation on two sides, 12 h. [b] Isolated yields. [c] Yields were determined by ^{1}H-NMR.

which has a trisubstituted alkene group, the reaction took place at the *in situ* formed terminal alkene due to the steric effect. Cyclobutane aldehyde could also be tolerated (Table 3, substrate **30**). For cyclopropane aldehyde, a subsequent ring-opening reaction occurred and provided product **31** in 59% yield, thus suggesting a radical process for this cascade reaction (Table 3, substrate **31**).

Then, we probed different ketones. Both linear and cyclic ketones proved to be suitable substrates. Different sized cyclic ketones worked efficiently and provided the products in moderate to good yields (Table 4, substrates **32–35**). Acetophenone and 3-acetylthiophene worked smoothly (Table 4, substrates **36** and **37**). Other linear ketones also provided the products in good yields (Table 4, substrates **38–42**).

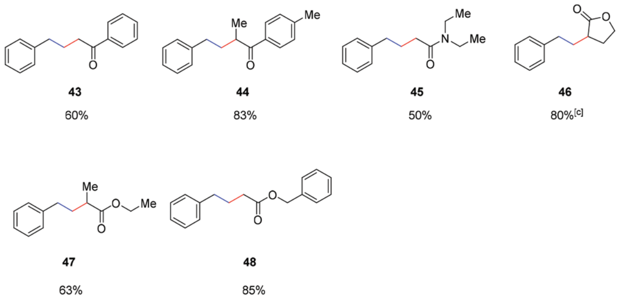
Finally, we surveyed the scope of thiols (Table 5). Different ketones (Table 5, substrates **43** and **44**), amide (Table 5, substrate **45**), lactone (Table 5, substrate **46**) and esters (Table 5, substrates **47** and **48**) bearing α-sulfide were efficiently converted to the corresponding products in moderate to good yields.

Table 4 Substrate scope for the cascade reaction[a,b]



[a] Reaction conditions: Ketone (1.0 mmol), ylide (1.2 mmol), 2-mercaptoacetate (2.0 mmol), DTBP (4.0 mmol), PPh_3 (2.5 mmol), DMSO–DCM (4 mL : 4 mL), room temperature, 55 W household CFL bulb irradiation on two sides, 12 h. [b] Isolated yields.

Table 5 Substrate scope for the cascade reaction[a,b]



[a] Reaction conditions: Benzaldehyde (1.0 mmol), ylide (1.2 mmol), sulfide (2.0 mmol), DTBP (4.0 mmol), PPh_3 (2.5 mmol), DMSO–DCM (4 mL : 4 mL), room temperature, 55 W household CFL bulb irradiation on two sides, 12 h. [b] Isolated yields. [c] Yields were determined by ^{1}H-NMR.

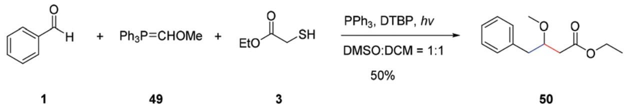


Fig. 2 Cascade reaction with Wittig reagent **49**.

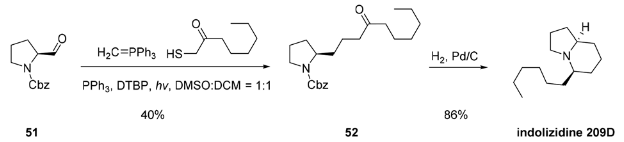


Fig. 3 Synthesis of **indolizidine 209D** *via* the cascade reaction.

We also tested other Wittig reagents such as compound **49**. We were able to isolate the desired product, albeit with a lower yield, probably due to the steric hindrance (Fig. 2).

To demonstrate the synthetic utility of this cascade reaction, we performed the synthesis of **indolizidine 209D**.[8] From commercially available aldehyde **51**, we were able to obtain compound **52** in one step with 40% yield *via* the cascade reaction. The following hydrogenation furnished the product in 86% yield. Thus, **indolizidine 209D** was synthesized over two steps with 34% yield (Fig. 3).

Conclusions

In conclusion, we have developed a novel cascade Wittig/hydroalkylation reaction induced by visible light. This green and metal-free radical process proceeds under mild conditions and tolerates a variety of functional groups. It allows access to saturated C3 homologation products directly from aldehydes or ketones *via* radical hydroalkylation to olefins, thus providing a useful tool for synthetic chemists.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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