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Multistep One-Pot Wittig/Nazarov Reaction for Construction of Cyclopentenone with Diazo Compounds and Acid Chlorides

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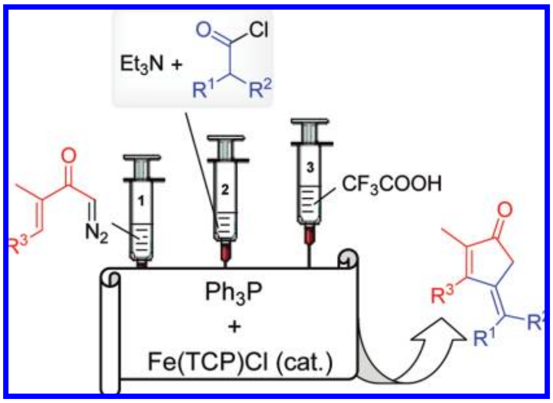
ABSTRACT



A facile multistep one-pot synthesis of single or fused cyclopentenones has been developed. The sequence involves a transition metal-catalyzed ylide formation/Wittig Olefination/Nazarov Cyclization.

The design and implementation of new economically sustainable synthetic processes is one of the major challenges in modern organic synthesis. The application of cascade or domino[1] and tandem[2] reactions in a "one-pot" manner offers a straightforward method for the construction of new bonds simultaneously or in a stepwise manner without the isolation of the intermediates, making the whole procedure economically sustainable and environmentally conscientious. Nowadays, multistep one-pot reactions have emerged as valuable tools in organic synthesis for reducing operative steps, simplifying purification procedures and enhancing synthetic efficiency,

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(1) For selected reviews: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Ikeda, S.-I. *Acc. Chem. Res.* **2000**, *33*, 511. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (d) Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2007**, *13*, 7280. (e) Enders, D.; Grondal, C.; Matthias, H. R. M. *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (f) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (g) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (h) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (i) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (j) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514. (k) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516.

(2) (a) Ho, T.-L. *Tandem Organic Reactions*; John Wiley & Sons, New York, 1992. For recent reviews on tandem reactions, see: . (b) Tejedor, D.; Gonzalez-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; de Armas, P.; Garcia-Tellado, F. *Chem.—Eur. J.* **2005**, *11*, 3502. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Guo, H.; Ma, J. *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (e) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (f) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (g) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (h) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (i) Hussain, M. M.; Patrick, J. W. *Acc. Chem. Res.* **2008**, *41*, 883. (j) Li, Z.; Chad, B.; He, C. *Chem. Rev.* **2008**, *108*, 3239.

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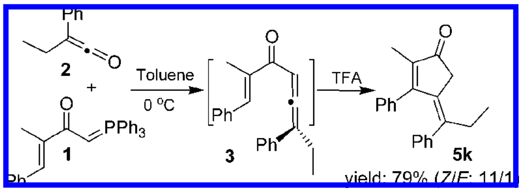
which saves solvents and resources. However, it is difficult to efficiently and chemoselectively control one-pot, multistep reactions, due to the mutual interference among various components. Herein, we report a successful example of multistep one-pot synthesis of β-methylenecyclopentenones through the Wittig/Nazarov reactions using unsaturated diazocarbonyl compounds and acyl chloride as the precursors of vinyl allenes.

As our ongoing research project on ylide chemistry,[3] we recently developed a novel efficient method of allene synthesis via transition metal-catalyzed reaction of diazocarbonyl compounds with phosphines and ketenes[4] in which a variety of di- and trisubstituted allenes can be obtained by olefination of ketenes with EDA in the presence of Ph_3P and tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(TCP)Cl). Allenes, owing to their unique chemical properties, are demonstrated as important synthetic building blocks in various reactions such as cycloadditions, cycloisomerizations, cross-coupling reactions and the Nazarov reaction.[5−10] The first Nazarov cyclization of an allenyl ketone was reported by Tius and Nagao independently.[6] In 1998, Hashmi extended this reaction to allenyl vinyl ketones, which delivered the products on silica gel.[7] In addition, indol-2-yl allenyl ketones were cleanly converted to the corresponding cyclopenta[b]-indole derivatives under mild conditions.[8] A variant type of Nazarov cyclization was reported by de Lera et al. in which divinylallene acetals underwent cyclization almost quantitatively under mild conditions (TsOH).[9] The cationic cyclopentannulation of allenyl ethers has been widely studied by Tius and constitutes a very efficient construction of α-methylenecyclopentenones.[10] We reasoned that allenyl vinyl ketones could be synthesized from the Wittig reaction of unsaturated carbonyl ylide with ketenes and might undergo cyclization efficiently in one pot.

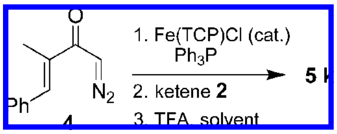
Initial attempts were made using unsaturated carbonyl ylide **1** and ketene **2** in toluene at 0 °C. The intermediate vinyl allenyl ketone **3**, detected by ^{1}H NMR, subsequently underwent cyclization under acidic conditions. Among several acids (TfOH, HCl, AcOH, $FeCl_3$ and silica gel) examined, TFA (40 equiv) was found to be the best giving the product in 79% yield with *Z*/*E* ratio of 11/1 (Scheme 1).

Scheme 1. One-Pot Reactions of Ylide **1** with Ketene **2**



Although Hashmi[7] and Forest[10f] have shown that silica gel can serve as an excellent catalyst for Nazarov cyclizations of allenyl vinyl ketones, it was not the optimal in the current case probably due to the interference of the in situ produced Ph_3PO. Considering the synthetic difficulty of pure unsaturated carbonyl ylide **1**, we discovered that the in situ generated **1** via Fe(TCP)Cl-catalyzed reaction of diazocarbonyl compounds **4** with Ph_3P reacted with ketene **2** as well as pure **1**. As shown in Table 1, the reactions proceeded better in ether

Table 1. Effect of Reaction Conditions on the One-Pot Wittig/Nararov Cyclization[a]



entry	solvent	equiv of TFA	*Z*/*E*[b]	yield[c] (%)
1	EtOH	40	11/1	81
2	CH_3CN	40	20/1	72
3	CH_2Cl_2	40	8/1	63
4	Et_2O	40	13/1	93
5	THF	40	9/1	88
6	DME	40	7/1	91
7	Et_2O	10	5/1	78
8	Et_2O	20	8/1	79
9	Et_2O	30	11/1	84
10	Et_2O	80	8/1	69
11[d]	Et_2O	40	12/1	95

[a] Conditions: a solution of diazo compound in toluene (2 mL) was slowly added in 2 h via a syringe pump to a solution of Ph_3P (1.2 equiv) and 1.0 mol % Fe(TCP)Cl in toluene (0.5 mL), 2 h at 0 °C and then quenched with the solution of TFA. [b] Determined by 300 MHz ^{1}H NMR. [c] Isolated yield. [d] Ketene was prepared in situ from acid chloride and Et_3N in 2 h at room temperature. For detailed procedure, see Supporting Information.

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(3) (a) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (b) Deng, X.-M.; Cai, P.; Ye, S.; Sun, X.-L.; Liao, W.-W.; Li, K.; Tang, Y.; Wu, Y.-D.; Dai, L.-X. *J. Am. Chem. Soc.* **2006**, *128*, 9730. (c) Cao, P.; Sun, X.-L.; Li, C.-Y.; Kang, Y.-B.; Xie, Z.; Tang, Y. *J. Org. Chem.* **2007**, *72*, 6628. (d) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem.* **2007**, *119*, 6055; *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (e) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408.

(4) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494.

(5) For recent reviews: (a) Zimmer, R.; Reissig, H.; *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; WILEY-VCH: Weinheim, 2004; Vol. 2, p 847. (b) Horvath, A.; Baeckvall, J. E. *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; WILEY-VCH: Weinheim, 2004; Vol. 2, pp 973−994. (c) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. For recent examples: (e) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem.* **2005**, *117*, 5409; *Angew. Chem., Int. Ed.* **2005**, *44*, 5275. (f) Trillo, B.; Lopez, F.; Gulias, M.; Castedo, L.; Mascarenas, J. L. *Angew. Chem.* **2008**, *120*, 965; *Angew. Chem., Int. Ed.* **2008**, *47*, 951. (g) Cheong, P. H.; Morganelli, P.; Michael, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517. (h) Lu, Z.; Zheng, S.; Zhang, X.; Lu, X. *Org. Lett.* **2008**, *10*, 3359. (i) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254. (j) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232. (k) Yudha, S. S.; Yoichiro, Y. T.; Takai, K. *Angew. Chem.* **2008**, *120*, 9458; *Angew. Chem., Int. Ed.* **2008**, *47*, 9318. (l) Alexander, S. D.; Anna, W. S.; Marina, R.; Joseph, T. K.; Alexander, V. K.; Vladimir, G. *J. Am. Chem. Soc.* **2008**, *130*, 1440.

(6) (a) Nagao, Y.; Lee, W.-S.; Kim, K. *Chem. Lett.* **1994**, 389. (b) Nagao, Y.; Lee, W.-S.; Kim, K. *Chem. Lett.* **1994**, 597. (c) Tius, M. A.; Kwok, C.-K.; Gu, X.-Q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871.

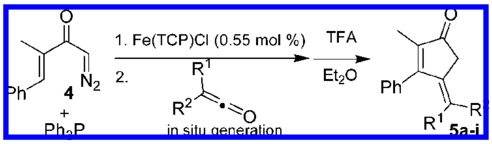
(7) Hashmi, A. S. K.; Bats, J. W.; Choi, J. H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491.

(8) (a) Ishikura, M.; Matsuzaki, Y.; Agata, I. *Chem. Commun.* **1996**, 2409. (b) Ishikura, M.; Uchiyama, H.; Matsuzaki, N. *Heterocycles* **2001**, *55*, 1063.

(9) (a) de Lera, A. R.; Rey, J. G.; Hrovat, D.; Iglesias, B.; Lopez, S. *Tetrahedron Lett.* **1997**, *38*, 7425. (b) Iglesias, B.; de Lera, A. R.; Rodriguez-Otero, J.; Lopez, S. *Chem.*−*Eur. J.* **2000**, *6*, 4021.

solvents, particularly in Et_2O (entry 4). On the other hand, the amount of TFA also had some effects on the yields and *Z/E* ratios of the cyclization. Furthermore, ketene **2** prepared in situ from 2-phenylbutanoyl chloride and Et_3N also worked extremely well in such a tandem Wittig/Nazarov cyclization to afford the product in nearly quantitative yield with a similar stereoselectivity, implying no interference of byproducts Et_3N•HCl or Ph_3PO to the reaction (entry 11). Subsequent investigation showed that the aforementioned method was applicable to various aryl alkyl ketenes. As indicated in Table 2, the nature of alkyl substituents on ketenes had little influence on the yields (entries 1−3). Ketene with homoallyl group reacted smoothly to give alkenyl cyclopentenone in good yield (entry 4). The steric and electronic effects of substituents on aryl ring had some influence on the yields (entries 5−8). Diaryl substituted ketene also gave good yield (entry 9). Ketene derived from cyclohexanecarboxylic acid did not work (entry 10). High *Z/E* ratios of the exocyclic alkene were observed in all products, except for **5a** (entry 1).

Table 2. One-Pot Synthesis of *β*-Methylenecyclopentenones **5a−i** from **4** and Acid Chlorides[a]

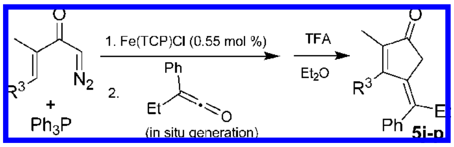


entry	product	R^1	R^2	Z/E[b]	yield (%)[c]
1	**5a**	C_6H_5	Me	2.5/1	90
2	**5b**	C_6H_5	*n*-Pr	12/1	86
3	**5c**	C_6H_5	*n*-Bu	10/1	88
4[d]	**5d**	C_6H_5	homoallyl	40/1	76
5	**5e**	*p*-MeO-C_6H_4	Et	10/1	84
6	**5f**	*p*−Cl-C_6H_4	Et	18/1	93
7[e]	**5g**	*p*−Br-C_6H_4	Et	9/1	65
8[f]	**5h**	1-naphthyl	Et	23/1	59
9	**5i**	Ph	Ph	−	68
10	−	cyclohexyl		−	trace

[a] Conditions: a solution of diazo compound in toluene (2 mL) was slowly added within 2 h via a syringe pump to a solution of Ph_3P (1.2 equiv) and 0.55 mol % of Fe(TCP)Cl in toluene (0.5 mL). Ketene was generated in situ from acid chloride and Et_3N in 2 h at room temperature, 2 h at 0 °C and then quenched with the solution of 40 equiv of TFA in 2.5 mL Et_2O. [b] Determined by 300 MHz ^1H NMR. [c] Isolated yield. [d] Ketene was generated in situ in 40 min. [e] Ketene was generated in situ in 1 h. [f] Ketene was generated in situ within 5 h at 40 °C.

Encouraged by the successful tandem Wittig/Nazarov reaction of **4**, a serious of conjugate unsaturated diazocarbonyl substrates were prepared to further investigate the reaction scope. As shown in Table 3, a wide range of vinyl diazoketones underwent cyclization smoothly in good yields with high *Z/E* ratios. Such method can also be used to prepare fused carbocyclic rings from 1-cyclohexenyl-2-diazoethanone in excellent yields with very good stereoselectivity, which adds to the versatility of the process (Scheme 2).

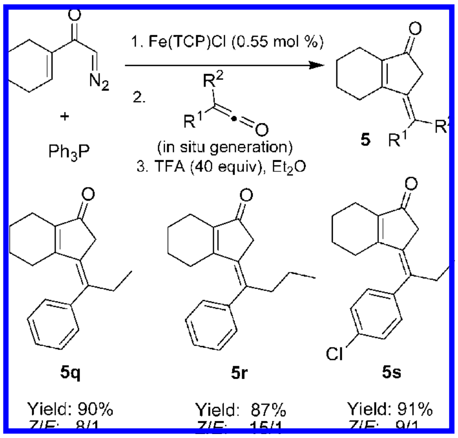
Table 3. Tandem Wittig/Nazarov Cyclization with Alkenyl Diazoketones[a]



entry	products	R^3	Z/E[b]	yield (%)[c]
1	**5j**	*p*-$MeOC_6H_4$	10/1	87
2	**5k**	C_6H_5	12/1	95
3	**5L**	*p*-ClC_6H_4	17/1	82
4	**5m**	2-furyl	15/1	80
5	**5n**	$C_6H_4CH{=}CH$	24/1	71
6	**5o**	C_5H_{11}	15/1	90
7[d]	**5p**	Cyclohexyl	11/1	63

[a] Conditions: a solution of diazo compound in toluene (2 mL) was slowly added in 2 h via a syringe pump to a solution of Ph_3P (1.2 equiv.) and 0.55 mol % of Fe(TCP)Cl in toluene (0.5 mL). Ketene was generated in situ from acid chloride and Et_3N within 2 h at room temperature, 2 h at 0 °C and then quenched with the solution of 40 equiv of TFA in 2.5 mL Et_2O. [b] Determined by 300 MHz ^1H NMR. [c] Isolated yield. [d] 1.1 mol % of Fe(TCP)Cl, diazo compound was slowly added in 3 h via a syringe pump.

Scheme 2. One-Pot Synthesis of Hexahydroindenone from 1-Cyclohexenyl-2-diazoethanone



Attempts to determine the *Z/E* selectivity of the cyclization products by ^1H NMR techniques were unsuccessful due to the invisible NOE. Fortunately, the molecular structures of the major isomers of products **5f** and **5q** were established by single-crystal X- ray analyses (Figure 1), which showed that the Nazarov cyclization reactions favored *Z* selectivity.[11]

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(10) (a) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 8985. (b) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447. (c) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509. (d) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091. (e) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (f) Forest, J.; Bee, C.; Cordaro, F.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4069. (g) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (h) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328. (j) Banaag, A. R.; Tius, M. A. *J. Org. Chem.* **2008**, *73*, 8133.

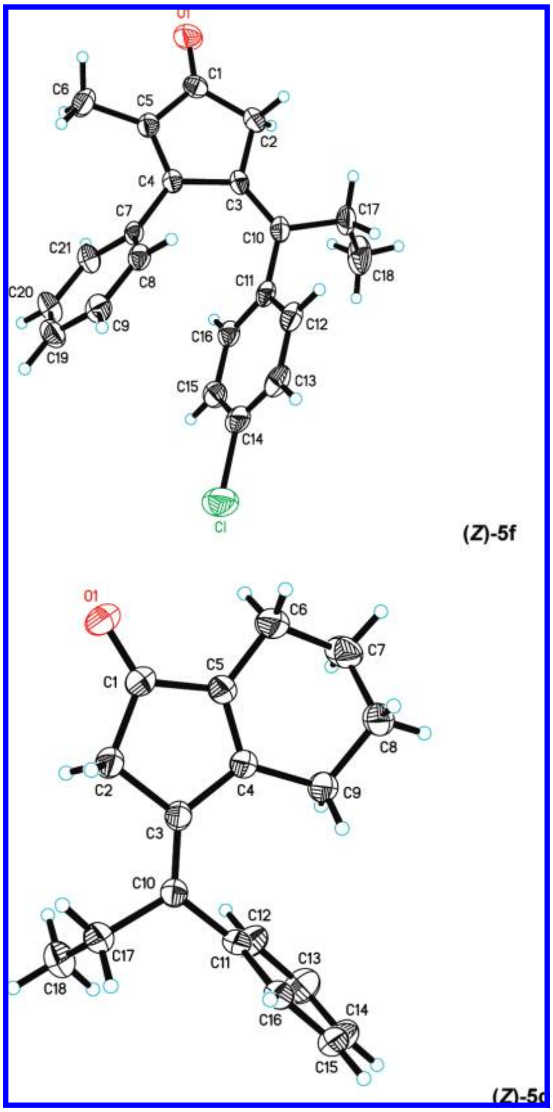
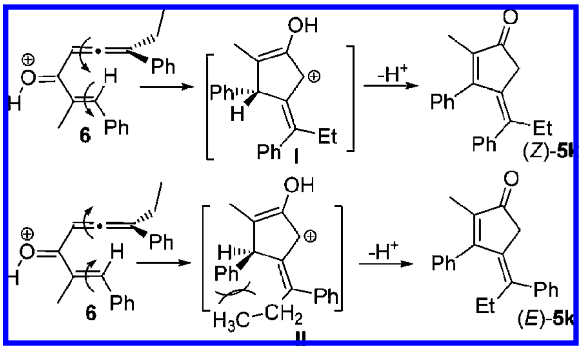


Figure 1. X-ray structures of the major isomers of **5f** and **5q**.

Scheme 3. Proposed Stereochemical Model



The high stereoselectivity can be explained very well as shown in Scheme 3. The cyclization proceeded via conrotation ring closure. Since the produced intermediate **I** is more stable than intermediate **II** due to the steric effect, *Z*-product were obtained as the major ones.[12]

In conclusion, we have developed a novel Wittig/Nazarov cyclization reaction, which offers a straightfoward method for the construction of β-methylenecyclopentenones in a multistep one-pot manner without the isolation of intermediates. The high yield, excellent stereoselectivity, mild reaction conditions as well as simple purification procedures make this method very attractive to the synthesis of cyclopentenone derivatives.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] CCDC 714457 (**5f**) and CCDC 714458 (**5q**) contain the supplementary crystallographic data.

[12] *E*-**5k** didn't isomerize into *Z*-**5k** under the reaction conditions.