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Alkynyl Group as Activating Group: Base-Catalyzed Diastereoselective Domino Reactions of Electron-Deficient Enynes

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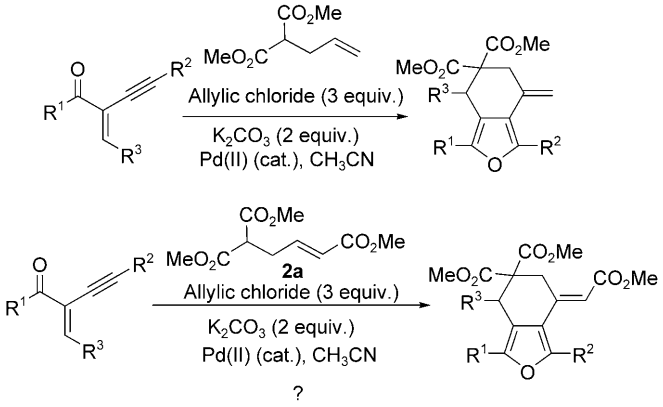
Abstract: This paper describes a base-catalyzed domino reaction of electron-deficient enynes with malonate-derived α,β-unsaturated esters and ketones, which provides a rapid, stereoselective access to multi-functionalized cyclopentanes and inden-5-(6*H*)-ones in high yields. In this reaction, the alkynyl group of the enyne acts as an activating group rather than a reacting group.

Keywords: alkynes; cyclohexanes; cyclopentanes; domino reactions; Michael reaction; stereoselectivity



Scheme 1. Reaction design.

Domino reactions take an important place in synthetic chemistry, since they provide a rapid and efficient access to architecturally complex molecules from relatively simple starting materials by combination of several transformations into one-step.[1] Recently, tandem reactions triggered by Michael addition have attracted interest of many chemists.[1g–j,2] In the context of our ongoing efforts to develop novel chemistry of electron-deficient enynes,[3,4] we report herein a novel base-catalyzed domino reaction consisting of double Michael additions of electron-deficient enynes for the rapid construction of highly functionalized cyclopentanes[5] and hexahydro-1*H*-inden-4(2*H*)-ones.

Recently, we described a palladium-catalyzed tandem reaction of 2-(1-alkynyl)-2-alkene-1-ones with 2-allylmalonate in the presence of allylic chloride to produce 5,6-bicyclic furans (Scheme 1). We envisaged that a bicyclic furan might be formed if crotonate-derived malonate **2a** was used instead of a 2-allylmalonate under the same conditions.[3c]

Initially, we examined the reaction of **1a** and **2a** in the presence of allyl chloride (3 equiv.) and K_2CO_3 (2 equiv.) under the catalysis of $PdCl_2(CH_3CN)_2$. To our surprise, the products were cyclopentane **3a** and its diastereomer **4a** *via* a tandem double Michael addition reaction rather than a 5,6-bicyclic furan. Further studies showed that this reaction could proceed in the presence of only a catalytic amount of base (Table 1). After some attempts, we were pleased to find that the reaction proceeded smoothly under the catalysis of 10 mol% of DBU in acetone at room temperature (entry 6, conditions A) to give the products **3a**/**4a** in combined 95% isolated yield but the diastereoselectivity is only 1/1.9, while a much better selectivity (1/7.8) of **3a**/**4a** could be obtained in 88% isolated yield under the catalysis of *t*-BuOK in THF (entry 8, conditions B). The structures of **3a** and **4a** were confirmed by X-ray crystallographic analysis (Figure 1).[6] Considering that there are three stereogenic centers in the product, the diastereoselectivity is quite good.

With the optimal reaction conditions in hand, we next turned our attention to studying the scope of enyne **1** (Table 2). Generally, the reaction proceeded

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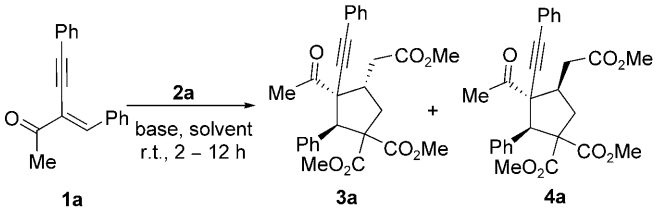
Table 1. Screening conditions for tandem reaction of **1a** with **2a**.



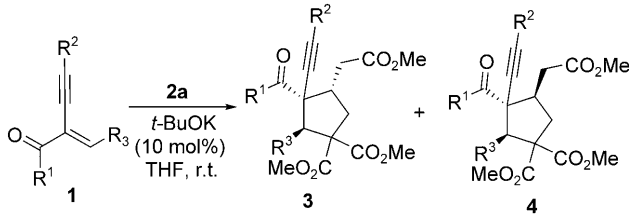
1a 3a 4a

Entry[a]	Base (10 mol%)	Solvent	Isolated yields of **3a/4a** [%]
1	NaH	THF	14/54
2[b]	DBU	THF	4/21
3	DBU	DMSO	11/58
4	DBU	CH_2Cl_2	12/19
5	DBU	toluene	15/24
6	DBU	CH_3COCH_3	33/62
7[b]	K_2CO_3	CH_3COCH_3	11/72
8[b]	*t*-BuOK	THF	10/78
9[b]	Cs_2CO_3	THF	11/79

[a] All the reactions were carried out using **1a** (0.33 mmol), **2a** (0.3 mmol) and 10 mol% of base at room temperature for 2–12 h.
[b] A trace amount of another diastereomer was detected by ^{1}H NMR analysis of the crude product.

smoothly to afford the corresponding products in moderate to excellent yields in high diastereoselectivity. It is interesting to find that the reactions of enynes **1e–1g** and **1i–1j** gave only one diastereomer (>20:1) (entries 5–7, 9–10). It is also noteworthy that the reaction of enyne **1c** with an ester group could

Table 2. Synthesis of mutifunctionalized cyclopentanes.



Entry[a]	$R^1/R^2/R^3$ (Enyne **1**)	Time [h]	Isolated yields of **3**, **4** [%]
1	Me/Ph/Ph (**1a**)	4	**3a** (10), **4a**(78)[b]
2	Ph/Ph/Ph (**1b**)	48	**3b** (11), **4b** (66)[b]
3	MeO/Ph/Ph (**1c**)	96	**3c** (8), **4c** (76)
4	Me/Ph/4-$MeOC_6H_4$ (**1d**)	12	**4d** (84)[b]
5	Me/*n*-Bu/Ph (**1e**)	14	**4e** (65)[e]
6	Me/1-naphthyl/Ph (**1f**)	10	**4f** (73)[e]
7[c]	Me/4-$NO_2C_6H_4$/Ph (**1g**)	6	**4g** (36)[e]
8	Me/4-$MeOC_6H_4$/Ph (**1h**)	14	**4h** (70)[b]
9	Me/Ph/*n*-Bu (**1i**)	3.5	**4i** (79)[e]
10	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1j**)	4	**4j** (92)[e]
11	Ph/4-$MeOC_6H_4$/Ph (**1k**)	12	**3k** (9), **4k** (68)
12	Ph/Ph/4-$MeOC_6H_4$ (**1l**)	12	**3l** (8), **4l** (61)
13[d]	4-ClC_6H_4/Ph/Ph (**1m**)	2	**3m** (27), **4m** (64)

[a] Unless specified, all the reactions were carried out at room temperature in 0.3 mmol scale under conditions B.
[b] A trace amount of diastereomer was detected by ^{1}H NMR analysis of the crude product.
[c] The solution of **1g** was added by syringe pump through **1h** and then stirred for another 5 h, a significant amount of by-product from the dimerization of **1g** was isolated.
[d] The reaction was run under conditions A.
[e] No other diastereomer was formed.

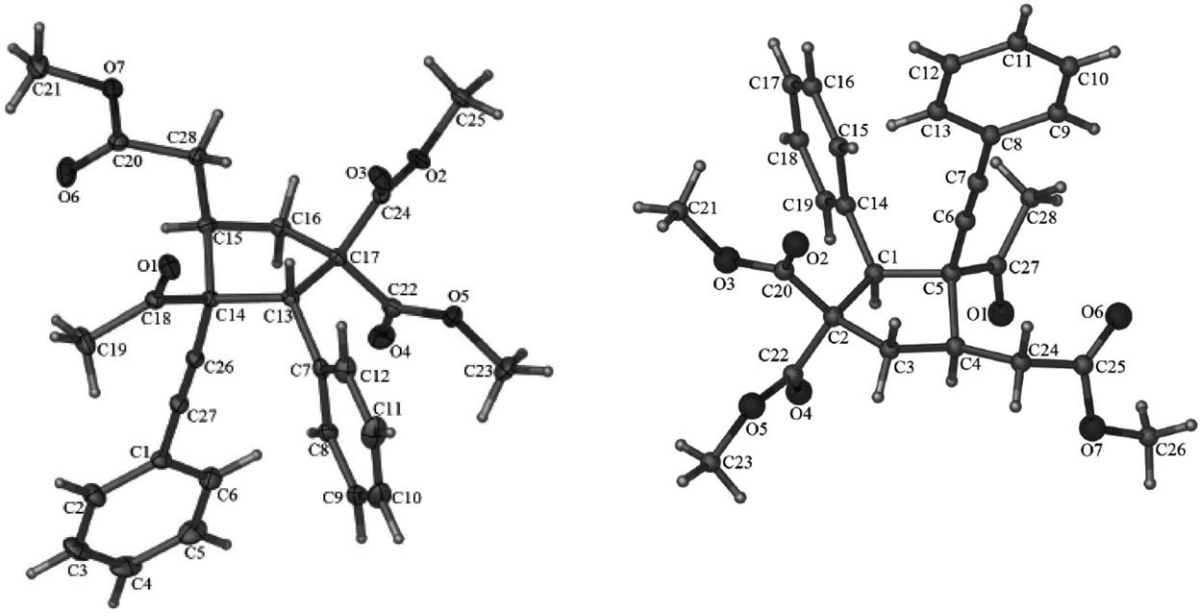


Figure 1. X-ray structures of **3a** (*left*) and **4a** (*right*).

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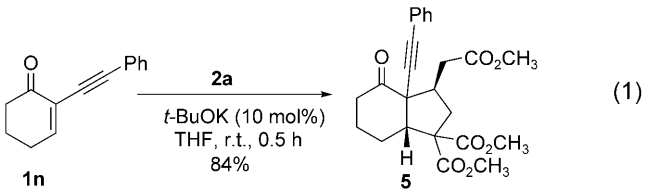
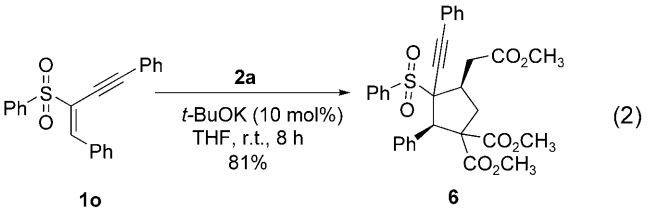
also give the desired product **4c** in high yield (76%) with 8% yield of its diastereomer **3c** (entry 3).

The reaction of a cyclic yne-enone **1n** with **2a** produced the desired fused 5,6-bicyclic product **5** in 63% yield after stirring the reaction mixture for 0.5 h under conditions B [Eq. (1)]. Enyne **1o** with a phenylsulfonyl moiety as the electron-withdrawing group reacted with **2a** under condtions B to give the corresponding product **6** in 81% yield [Eq. (2)]. Multifunctionalized cyclohexanes could be obtained in 63% yield from the reaction of **1a** with substrate **2b** [Eq. (3)].



(1)



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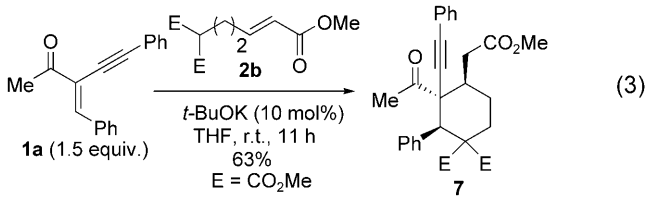
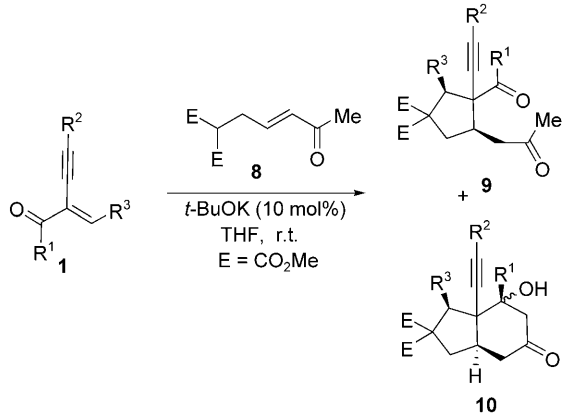


(3)

We next examined the domino reaction of yne-enone **1a** with malonate-derived α,β-unsaturated ketone **8** and the results are summarized in Table 3. It is interesting to find that the reaction of **1a** with **8** proceeded smoothly to give a multi-functionalized bicyclic hexahydro-1*H*-inden- 4(2*H*)-one **10a** as two separable diastereomers in 87% total yield after 4 h *via* novel tandem double Michael additions and aldol reaction (entry 1), The relative stereochemistry of the minor diastereomer of **10a** was further confirmed by X-ray crystallographic analysis (Figure 2)[6]. Multifunctionalized cyclopentanes **9** could be also obtained by running the reaction for a shorter time. For example, the reaction of **1b** with **8** gave cyclopentane **9b** in 62% yield along with 20% of bicyclic inden-5 (6*H*)-one **10b** after reacting for 2 h. In contrast, only 9% yield of **9b** along with a higher yield of **10b** were obtained after 12 h, indicating that **9b** could convert into **10b** slowly under the reaction conditions (entries 2 and 3). It is noteworthy that those R^1 = Ph substrates such as **1b**, **1l**, **1p** could give the desired inden-5 (6*H*)-ones **10b**, **10l** and **10p** as a single diastereomer, respectively (entries 3, 8 and 9).

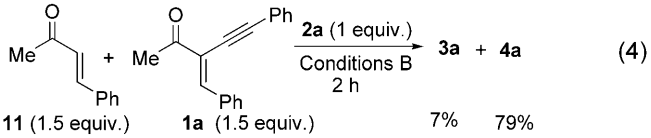
Table 3. Product control in tandem reactions of enyne **1** with **8**.



Entry[a]	$R^1/R^2/R^3$ (Enyne **1**)	Time [h]	Isolated yields of **9**, **10** [%][b]
1	Me/Ph/Ph (**1a**)	4	**9a** (–), **10a** (59/28)
2	Ph/Ph/Ph (**1b**)	2	**9b** (62)[c], **10b** (20)
3	**1b**	12	**9b** (9)[c], **10b** (68)
4	Me/4-$NO_2C_6H_4$/Ph (**1g**)	12	**9g** (16), **10g** (66/4)
5	Me/4-$MeOC_6H_4$/Ph (**1h**)	12	**9h** (8), **10h** (67/25)
6	Me/4-$MeOC_6H_4$/4-$MeOC_6H_4$ (**1j**)	6	**9j** (20), **10j** (58/14)
7	Ph/Ph/4-$MeOC_6H_4$ (**1l**)	5	**9l** (49), **10l** (32)
8	**1l**	12	**9l** (10), **10l** (73)
9	Ph/*n*-Bu/Ph (**1p**)	16	**9p** (48/9), **10p** (37)

[a] All the reactions were carried out at room temperature in 0.3 mmol scale.
[b] Numbers in parenthesis are the isolated yields of the corresponding diastereoismers.
[c] Trace amount of another diastereomer was formed.

Interestingly, the reaction of **2a** with a mixture of yne-enone **1a** and enone **11** only gave cycloadducts **3a** and **4a**, in which no any cycloadducts of **11** with **2a** were detected [Eq. (4)]. This result indicates that the alkynyl group acts as an activating group by lowering the LUMO level to make yne-enone **1a** more active than the correponding enone **11**



(4)

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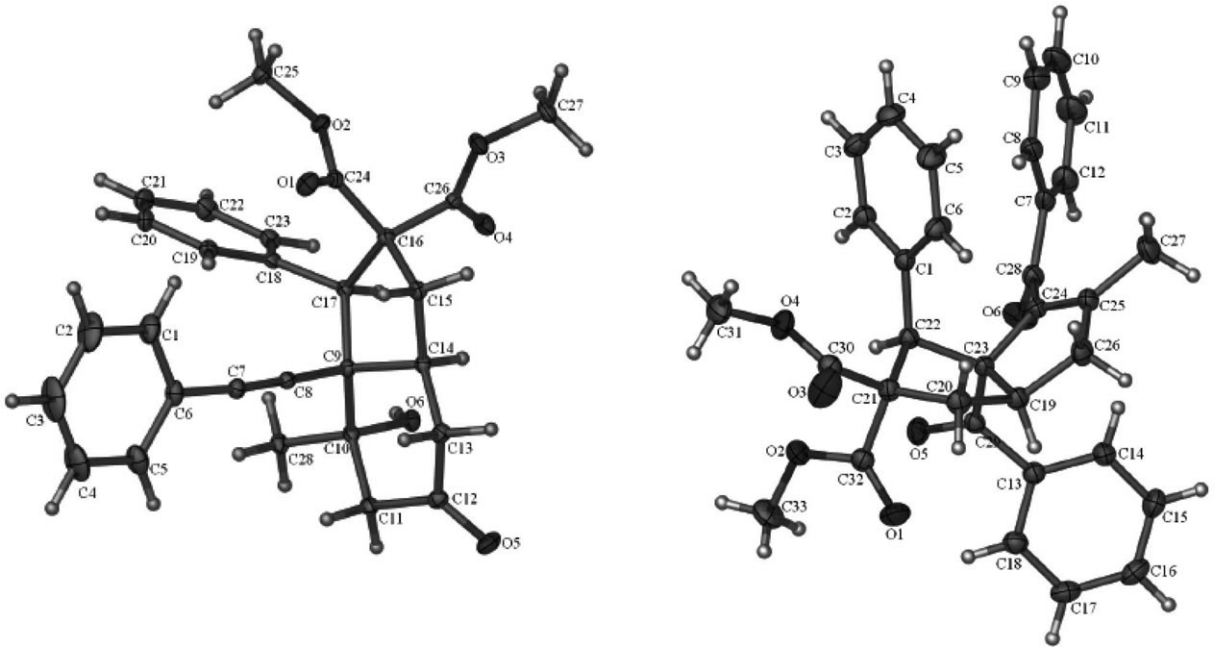
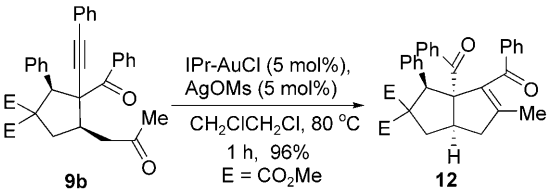


Figure 2. X-ray structures of the minor isomer of **10a** (*left*) and **12** (*right*).

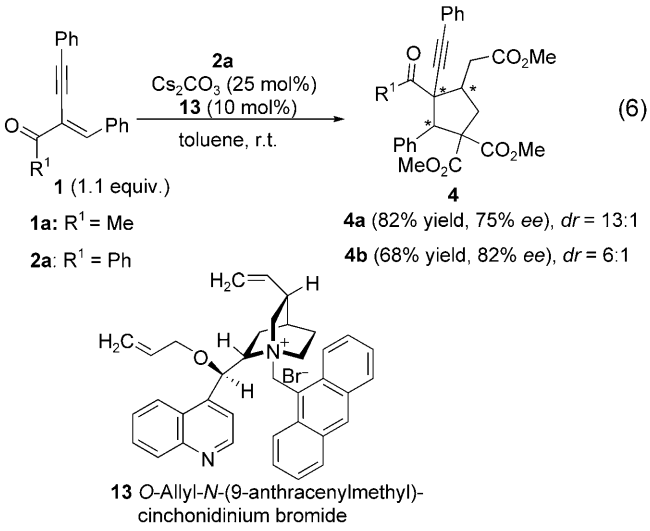
The synthetic utilities of compounds **9** were showcased by selective transformation of a representative product **9b**.[7] Compound **9b** could be converted into functionalized hexahydropentalene **12** in 96% yield by a gold(I)-catalyzed regioselective intramolecular alkyne-ketone metathesis [Eq. (5)].[8] The structure of



(5)

compound **12** was confirmed by X-ray crystallographic analysis (Figure 2).[6]

Pleasingly, an asymmetric version of the tandem reaction was achieved by application of a chiral phase-transfer catalyst. For example, the reaction of yne-enone **1a** and **2a** in the present of 25 mol% Cs_2CO_3 and 10 mol% cinchonidine-derived salt **13** in toluene at room temperature could give **4a**, **b** in 75% and 82% *ee*, respectively [Eq. (6)]. These results would male this reaction even more attractive.



(6)

One plausible mechanism for this base-catalyzed domino reaction of electron-deficient enynes with malonate-derived ketone is depicted in Scheme 2. Treatment of the malonate-derived α,β-unsaturated ketone **8** with the base produced stablized carboanoin intermediate **A**, which would undergo an intermolecular Michael addition to the yne-enone **1** to afford enolate **B/B′**. Subsquent intramolecular Michael addition of the enolate carboanion to the enone would give a new enolate intermediate **C**. It is possible that sterically less hindered alkynyl groups result in a "*cis*" orientation for the substituent R^3.[9] Protonation of the resulting intermediate **C** would produce cyclopentanes **9** and regenerate intermediate **A**. The intramolecular aldol reactions would produce the bicyclic inden-5 (6*H*)-ones **10**.

In summary, we have developed a base-catalyzed domino reaction of electron-deficient enynes with malonate-derived α,β-unsaturated esters or ketones, which provides a rapid, efficient and stereoselective access to multifunctionalized cyclopentanes, cyclohex-

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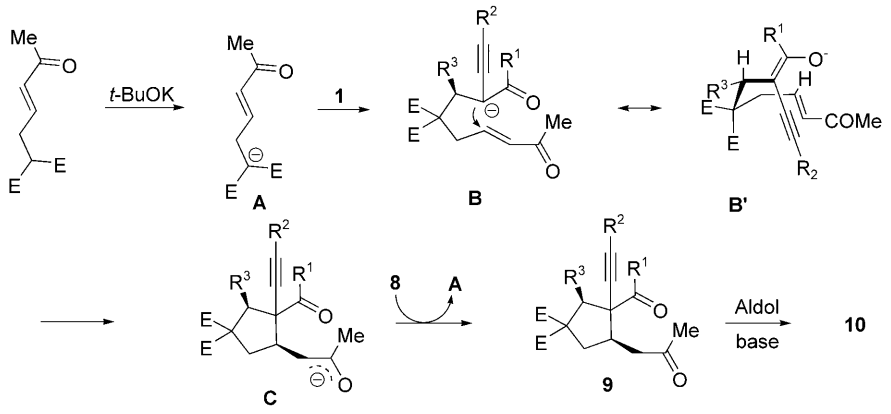

Scheme 2. Plausible mechanism.

anes and hexahydro-1*H*-inden-4(2*H*)-ones. It is noteworthy that the alkynyl group acts as an activating group to accelerate this domino transformation. Synthetic applications of this domino reaction are ongoing in this laboratory and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of Multifunctionalized Cyclopentanes and Cyclohexanes

Synthesis of 3a and 4a under conditions A: To a dry Schlenk tube, **2a** (69.0 mg, 0.3 mmol), **1a** (81.2 mg, 0.33 mmol), and DBU (4.6 mg, 10 mol%, 0.03 mmol) in acetone (2.5 mL) were added sequentially. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature. The reaction progress was monitored by TLC. The solvent was removed under vacuum, and the residue was purified by flash column (hexanes/ethyl acetate = 5:1) to afford compound **3a** (yield: 47.1 mg, 33%) and **4a** (yield: 88.5 mg, 62%), respectively.

Synthesis of 4j under conditions B: To a dry Schlenk tube, **2a** (69.0 mg, 0.3 mmol), **1j** (101.0 mg, 0.33 mmol), and *t*-BuOK (3.5 mg, 10 mol%, 0.03 mmol) in dry THF (2.5 mL) were added sequentially. The reaction mixture was allowed to stir under a nitrogen atmosphere at room temperature. The reaction progress was monitored by TLC. The solvent was removed under vacuum, and the residue was purified by flash column (hexanes/ethyl acetate = 5:1) to afford **4j**; yield: 148 mg (92%).

Supporting Information

Experimental details and copies of $^{1}H/^{13}C$ NMR spectra of all new compounds are available as supporting information.

Acknowledgements

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References

[1] For recent reviews of domino reactions, please see: a) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451; b) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; c) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095; d) T. J. J. Müller, in: *Topics in Organometallic Chemistry*, (Ed.: T. J. J. Müller), Springer Verlag, Berlin, **2006**, Vol. 19, p 149; e) *Domino Reactions in Organic Synthesis*, (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, Weinheim, **2006**, p 359; f) A. Padwa, S. K. Bur, *Tetrahedron* **2007**, *63*, 5341; g) D. J. Rammon, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602; h) H. Guo, J. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, *45*, 354; i) H. Pellissier, *Tetrahedron* **2006**, *62*, 2143; j) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

[2] For reviews of double Michael addition reactions, please see: a) M. Ihara, K. Fukumoto, *Angew. Chem.* **1993**, *105*, 1059; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010; b) R. B. Grossman, *Synlett* **2001**, 13. For leading examples of tandem double Michael additions, please see: c) J. Tan, X. Xu, L. Zhang, Y. Li, Q. Liu, *Angew. Chem.* **2009**, *121*, 2912; *Angew. Chem. Int. Ed.* **2009**, *48*, 2868; d) Z. Lu, G. Chai, S. Ma, *Angew. Chem.* **2008**, *120*, 6134; *Angew. Chem. Int. Ed.* **2008**, *47*, 6045; e) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12928; f) H. Li, L. Zu, H. Xie, J. Wang, W. Jiang, W. Wang, *Org. Lett.* **2007**, *9*, 1833; g) L. Zu, H. Li, H. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem.* **2007**, *119*, 3806; *Angew. Chem. Int. Ed.* **2007**, *46*, 3732; h) B. Tan, Z. Shi, P.-J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425; i) R. A. Bunce, E. J. Wamsley, J. D. Pierce, A. J. Shellhammer, Jr., R. E. Drumright, *J. Org. Chem.* **1987**, *52*, 464.

[3] For the work from our group, in which the alkynyl group is reacting group, please see: a) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.*

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2008, *47*, 1903; b) X. Yu, H. Ren, Y. Xiao, J. Zhang, *Chem. Eur. J.* **2008**, *14*, 8481; c) Y. Xiao, J. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 617; d) F. Liu, Y. Yu, J. Zhang, *Angew. Chem.* **2009**, *121*, 5613; *Angew. Chem. Int. Ed.* **2009**, *48*, 5505; e) R. Liu, J. Zhang, *Chem. Eur. J.* **2009**, *15*, 9303.

[4] For work from other groups in which the alkynyl group is also reacting group, please see: a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679; c) Y. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; d) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531.

[5] For reviews of the synthesis and bioactivities of cyclopentanes, please see: a) F. C. Biaggio, A. R. Rufino, M. H. Zaim, C. Y. H. Zaim, M. A. Bueno, A. Rodrigues, *Curr. Org. Chem.* **2005**, *9*, 419; b) G. Helmchen, M. Ernst, G. Paradies, *Pure Appl. Chem.* **2004**, *76*, 495; c) L. F. Silva, *Tetrahedron* **2002**, *58*, 9137; d) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; e) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293; f) B. Štefane, P. Brožič, M. Vehovc, T. L. Rižner, S. Gobec, *Eur. J. Med. Chem.* **2009**, *44*, 2563; g) B. Heasley, *Eur. J. Org. Chem.* **2009**, 1477.

[6] CCDC 742299 (**3a**), CCDC 742298 (**4a**), CCDC 742300 (the minor diastereomer of **10a**), and CCDC 747498 (**12**) contain 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.

[7] An Au(I)-catalyzed selective conversion of compounds **4** into cyclohexenes or 5,6-fused bicyclic compounds has been developed and these results will be reported in due course.

[8] Alkyne-ketone metathesis, please see: a) M. Curini, F. Epifano, F. Maltese, O. Rosati, *Synlett* **2003**, 552; b) J. U. Rhee, M. Krische, *Org. Lett.* **2005**, *7*, 2493; c) A. Saito, M. Umakoshi, N. Yagyu, Y. Hanazawa, *Org. Lett.* **2008**, *10*, 1783; d) G. S. Viswanathan, C.-J. Lee, *Tetrahedron Lett.* **2002**, *43*, 1613; e) C. González-Rodríguez, L. Escalante, J. A. Varela, L. Castedo, C. Saá, *Org. Lett.* **2009**, *11*, 1531; f) T. Jin, F. Yang, C. Liu, Y. Yamamoto, *Chem. Commun.* **2009**, 3533.

[9] T. Ishikawa, T. Aikawa, S. Watanabe, S. Saito, *Org. Lett.* **2006**, *8*, 3881.

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