Pergamon

Tetrahedron Letters 41 (2000) 1409–1412

TETRAHEDRON
LETTERS

A continuous Michael and aldol coupling of α,β-enones catalyzed by iridium complexes

Isamu Matsuda,* Tatsuya Makino, Yuki Hasegawa and Kenji Itoh

Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan

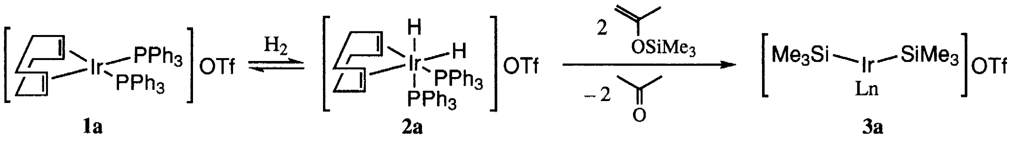
Received 20 October 1999; revised 22 November 1999; accepted 3 December 1999

Abstract

Ir[(COD)(PPh_3)$_2$]OTf activated by H_2 molecule catalyzes Michael-type coupling of α,β-enones with enoxysilanes to give 1,5-dicarbonyl compounds after the subsequent protodesilylation. An identical catalyst system makes it possible to attain a continuous Michael and aldol modification toward α,β-enones in a one-pot operation. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: iridium complex; Michael reaction; enoxysilanes; aldol reaction.

Michael-type reactions are widely recognized as a popular method for carbon–carbon bond formation.[1] In particular, the coupling of enoxysilanes with α,β-enones has attracted widespread interest in synthetic organic chemistry, since $TiCl_4$-mediated and trityl perchlorate-catalyzed methods were introduced by Mukaiyama.[2] If the resultant enolate ions or enoxysilane is available as a nucleophile, an α,β-enone would be modified at both the β- and α-positions by a one-pot cascade operation.[3] During our project to explore a new concept of carbon–carbon bond formation catalyzed by an Ir complex, we found that [Ir(COD)(PPh_3)$_2$]OTf (**1a**) activated by H_2 molecule is highly effective for the Mukaiyama-type aldol coupling.[4] The observation of ^{1}H NMR spectrum shows that **2a**, formed by the oxidative addition of H_2 to **1a**, reacts with two molecules of an enoxysilane to form a species including two Ir–Si bonds (**3a**). This complex would interact nucleophilically with acetals or aldehydes to form the Ir–C species which plays a role as a trigger of the aldol coupling.



(1)

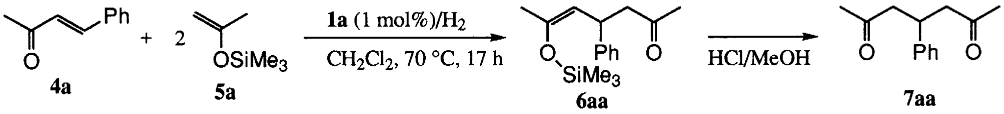
---

[*] Corresponding author. Fax: +81-52-789-5116; e-mail: matsudai@apchem.nagoya-u.ac.jp (I. Matsuda)

PII: S0040-4039(99)02304-7

According to the above generalization, **3a** may behave as a catalyst capable of Michael-type additions of enoxysilanes toward α,β-enones. In fact, this type of coupling is realized by using a catalyst system prepared from **1a**. We describe here an Ir(I)-catalyzed Michael-type coupling between α,β-enones and enoxysilanes, and the application to a consecutive modification of the β- and α-positions of α,β-enones.

Michael-type coupling product **7aa** was isolated after protodesilylation in 33% yield when a CH_2Cl_2 solution of benzalacetone (**4a**) and two equivalent moles of trimethylsilyloxypropene (**5a**) was heated for 13 h at 70°C in a sealed tube containing 1 mol% of **1a** which was preliminarily activated by H_2 molecule at −78°C. The ^{1}H NMR spectrum of the crude mixture obtained before protodesilylation suggests that the initial product of this reaction is the enoxysilane **6aa** which is difficult to isolate from a multi-component mixture. Though increase of the catalyst precursor **1a** (3 mol%) did not improve the isolated yield of **7aa**, the use of four equivalent moles of **5a** resulted a good yield of **7aa** (67%).



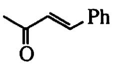
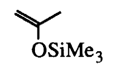
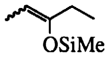
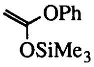
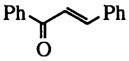
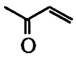
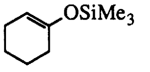
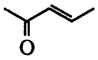
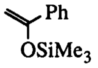
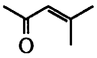
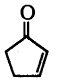
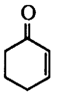
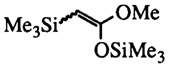
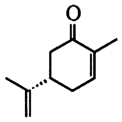
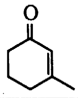
(2)

Despite the moderate yield of **7** at present, it is an important finding that the Michael-type coupling is also catalyzed by an identical system for aldol couplings. Thus, several combinations of α,β-enones and enoxysilanes were used to reveal the scope and limitations of the Michael coupling based on this concept. The results are summarized in Table 1.

Linear α,β-enones, **4a**, **4b**, **4c**, and **4d** reacted with **5** to give **7** in a yield of almost equal level, except a combination of **4c** and **5a** (entry 7). The substituent on the nucleophilic carbon of enoxysilanes may cause lowered reactivity for Michael-type coupling. For example, **5b** needed a higher concentration of the catalyst and prolonged reaction time to obtain **7ab** in an acceptable yield (entry 4). On the other hand, ketene acetal **5e** was more effective than **5a**. Two equivalent moles of **5e** were sufficient to obtain 68% of **7ae** (entry 5). α,β-Enones bearing two substituents on the β-carbon hindered severely the coupling (entry 11). Cyclic α,β-enones (**4f** and **4g**) gave the corresponding **7** in good to excellent yields under similar conditions with the reaction of **5**. In particular, **7ga** and **7gb** were isolated in 97% and 93% yield, respectively, in the reaction of **4g** with four equivalent moles of **5a** or **5b** (entries 14 and 17). The corresponding precursors, **6ga** and **6gb** were isolated by simple distillation. When ketene acetal **5e** was used as a nucleophile, a moderate yield of **7ge** was obtained in the reaction of **4g** with an equivalent mole of **5e** (entry 18). Although (*S*)-(+)-carvone (**4h**) resulted in poor conversion under similar conditions because of the two substituents on the cyclohexenone ring, the yield was improved by a slight modification of conditions, namely, high concentration of the catalyst and extended reaction time (entries 20 and 21). The substituent on the β-carbon of cyclic enones prevented severely the coupling (entry 22). Choice of the counter anion is also crucial for the success of the Michael couplings. Complexes, **1a** (X=OTf) and **1b** (X=ClO_4) showed almost similar efficiency as a catalyst, whereas **1c** (X=PF_6) resulted in poor yields of **7** (entries 1, 2, 3, 14, 15, and 16).

Mukaiyama aldol couplings and Michael-type couplings using enoxysilanes are successfully achieved by an identical Ir(I) cation complex. The structure of the resultant enoxysilane is retained in the step just before protodesilylation in the Ir-catalyzed Michael coupling. Thus, a one-pot modification toward α,β-enones is designed by a combination of Michael and aldol couplings. Into a CH_2Cl_2 solution containing **1a** (3 mol%) activated by H_2 molecule, were added **4g** and **5e** (1.3 equiv. moles) successively. After the completion of Michael coupling (50°C, 12 h), benzaldehyde dimethylacetal (1.3 mol equiv.) was added into the same reaction vessel. The resulting mixture was stirred for a further 24 h at 25°C to give 81% of **8a** after chromatographic purification. When other acetals such as dimethoxymethane and

Table 1
[Ir(COD)(PPh$_3$)$_2$]X (**1**) catalyzed Michael coupling of **4** with **5**[a]

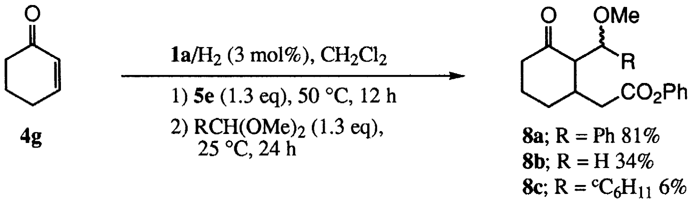
Entry	α,β-Enone	Enoxysilane	Ratio **4**:**5**	X of **1**	Mol% of **1**	Time (h)	Product	yield (%) [b]
1	**4a** 	**5a** 	1:4	OTf	1	13	**7aa**	67
2			1:4	ClO$_4$	1	15	**7aa**	50
3			1:4	PF$_6$	3	19	**7aa**	trace
4		**5b** 	1:4	OTf	5	88	**7ab**	56[c]
5		**5e** 	1:2	OTf	1	13	**7ae**	68
6	**4b** 	**5a**	1:2	OTf	1	19	**7ba**	68
7	**4c** 	**5a**	1:3	OTf	1	19	**7ca**	32
8		**5b**	1:3	OTf	1	16	**7cb**	62
9		**5d** 	1:4	OTf	1	12	**7cd**	60
10	**4d** 	**5c** 	1:3	OTf	1	14	**7dc**	66
11	**4e** 	**5a**	1:2	OTf	1	20	**7ea**	4
12	**4f** 	**5a**	1:4	OTf	1	16	**7fa**	76
13		**5b**	1:4	OTf	1	14	**7fb**	66[c]
14	**4g** 	**5a**	1:4	OTf	1	14	**7ga**	97
15		**5a**	1:4	ClO$_4$	1	14	**7ga**	99
16		**5a**	1:4	PF$_6$	1	14	**7ga**	10
17		**5b**	1:4	OTf	1	15	**7gb**	93[c]
18		**5e**	1:1	OTf	1	21	**7ge**	68
19		**5f** 	1:2.5	OTf	1	37	**7gf**	76[c]
20	**4h** 	**5a**	1:4	OTf	5	62	**7ha**	86[c]
21		**5a**	1:4	OTf	5	132	**7ha**	91[c]
22	**4i** 	**5a**	1:4	OTf	1	13	**7ia**	16

[a] The reactions were conducted on a 1 to 2 mmoles scale in a CH$_2$Cl$_2$ solution at 70 °C.

[b] Isolated yield after protodesilylation of **6**.

[c] Diastereomers are not specified at present.

cyclohexanecarboxaldehyde dimethylacetal are used as an acceptor of aldol coupling, the second step is the bottleneck giving insufficient yield of **8b** (34%) and **8c** (6% with the concomitant formation of the product (17%) resulted by the elimination of methanol from **8c**) despite the relatively severe conditions (50°C, 18 h).



4g

8a; R = Ph 81%
8b; R = H 34%
8c; R = ^{c}C$_6$H$_{11}$ 6%

(3)

In conclusion, we have found that [Ir(COD)(PPh$_3$)$_2$]OTf activated by H$_2$ molecule catalyzes Michael-type coupling between an α,β-enone and an enoxysilane and that the identical catalyst system enables a one-pot modification at β- and α-positions of α,β-enones.

References

1. (a) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; p. 139. (b) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; p. 169.
2. Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Narasaka, K.; Soai, K.; Aikawa, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779. (c) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163. (d) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. (e) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 953. (f) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472.
3. (a) Chepdelaine, M. J.; Hulce, M. *Org. Reactions* **1990**, *38*, 225. (b) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 221. (c) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 1805. (d) Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1986**, 1821. (e) Giuseppone, N.; Courtaux, Y.; Collin, J. *Tetrahedron Lett.* **1998**, *39*, 7845. (f) Yamada, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666.
4. Matsuda, I.; Hasegawa, Y.; Makino, T.; Itoh, K. *Tetrahedron Lett.*, in press.