A Novel One-Pot Iridium-Catalyzed Alder–Ene–Murahashi Sequence

Manuela Kummeter, Christian M. Ruff, Thomas J. J. Müller*[1]

Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax +49(211)8114324; E-mail: ThomasJJ.Mueller@uni-duesseldorf.de

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Dedicated to Prof. Dr. Wolfgang Beck on the occasion of his 75th birthday

Abstract: Yne allyl alcohols could be transformed under very mild conditions by a novel iridium-catalyzed one-pot cycloisomerization–Murahashi sequence in 43–77% yield.

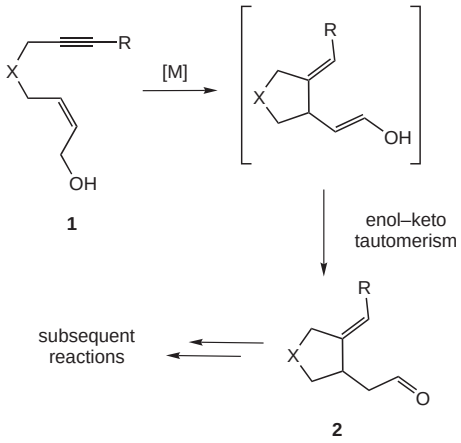
Key words: additions, alkynes, catalysis, condensations, ene reactions, iridium

In recent years economically and ecologically benign processes have become a playground for developing and inventing new methodologies. In particular, the use of one catalyst for more than one type of transformation in a one-pot fashion, generally referred to as sequential catalysis,[2] turns out to be catching two or more birds with one stone as well as conceptual elegant and highly practical. Although, among transition-metal-catalyzed sequences sequentially palladium-catalyzed processes are well-designed cascade reactions and experience quite recently an increasing interest,[3] for other metals this field has just been opened.[2,4]

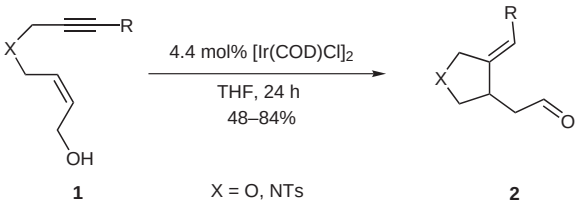
A group of transformations that are highly atom-economical are the transition-metal-catalyzed cycloisomerizations of enynes to generate cyclic dienes.[5] In comparison to palladium-,[5a–c] ruthenium-,[5d,e] and rhodium-catalyzed[5f–h] Alder–ene cycloisomerizations (AEC), iridium complexes[5i,j] are not that common, although, they have just recently become attractive in allylic alkylation[6] and Murahashi condensation.[7] The latter is a perfect example for a base- and acid-free aldol-type condensation.

As part of our program to design new sequences to complex molecules initiated by intramolecular Alder–ene cycloisomerizations of yne allyl alcohols to enals by virtue of the tautomerism of the dienol intermediate (Scheme 1),[8] we are particularly interested in sequentially catalyzed one-pot processes. Since Pd-catalyzed AEC reveal considerable drawbacks for aryl-substituted yne allyl alcohols, we sought for an alternative catalyst system. Here, we communicate a new sequential AEC–Murahashi condensation in a one-pot fashion and under mild conditions.

Therefore, we set out to test $[Ir(COD)Cl]_2$ as previously published for Alder–ene cycloisomerizations of enynes.[5i,j] According to the tentative mechanistic rationale occurring via an oxidative cyclization followed by β-hydride elimination and subsequent reductive elimination, neither the addition of an auxiliary carboxylic acid as for Pd(0) precursors nor the generation of air-sensitive cationic specimens as for Rh(I) complexes is necessary. Hence, upon reaction of yne allyl alcohols **1** in the presence of catalytic amounts of $[Ir(COD)Cl]_2$ in THF at room temperature the heterocyclic enals **2** are isolated in good yields (Scheme 2, Table 1).[9,10]



Scheme 1 Alder–ene cycloisomerizations of yne allylalcohols **1** to aldehydes **2** as an entry to sequential transformations



Scheme 2 Ir-catalyzed cycloisomerization of yne allyl alcohols **1** to enals **2**

Besides extensive spectroscopic analyses (^{1}H NMR, ^{13}C NMR and DEPT, COSY, and HETCOR NMR experiments, MS) the configuration of the double bond was initially determined by a NOESY experiment and later unambiguously confirmed by X-ray crystal structure analysis of the compound **2c** (Figure 1).[11]

Yne allyl alcohols with electronically variable aryl substituents can be transformed into the expected enaldehydes **2a**–**e** in good yields (Table 1, entries 1–13). However, aliphatic substituents even with variable steric and electronic demand fail to give the desired products

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(Table 1, entries 12–15). With this regard the Pd-catalyzed cycloisomerization is fully complementary, where the yne allyl alcohols **1f–i** can be efficiently transformed.[8a] Obviously, the presence of aryl substituents, presumably as a consequence of π-coordination regardless of the electronic nature of the aryl ring, seems to be essential for the transformation. Interestingly, independent from the configuration of the double bond of the yne allyl alcohol both diastereomers give the same yield (Table 1, entries 1 and 2). Other than Rh- or Pd-catalyzed AEC even the *trans*-configured yne allyl alcohol **1a** can be effectively transformed.

Table 1 Iridium-Catalyzed Cycloisomerization of Yne Allyl Alcohols **1** to γ,δ-Enals **2**[a]

Entry	X	R	Temp (°C)	Product	Yield (%)[b]
1	O	Ph	r.t.	**2a**	63
2[c]	O	Ph	r.t.	**2a**	60
3	O	Ph	60	**2a**	48
4	O	4-$MeOC_6H_4$	r.t.	**2b**	60
5	O	4-$MeOC_6H_4$	60	**2b**	58
6	O	4-$NO_2C_6H_4$	r.t.	**2c**	62
7	O	4-$NO_2C_6H_4$	60	**2c**	71
8	O	4-MeC_6H_4	r.t.	**2d**	71
9	O	4-MeC_6H_4	60	**2d**	73
10	TsN	Ph	r.t.	**2e**	78
11	TsN	Ph	60	**2e**	84
12	O	CH_2OMe	60	**2f**	–
13	O	Me	60	**2g**	–
14	O	CO_2Me	60	**2h**	–
15	O	TMS	60	**2i**	–

[a] Reaction conditions: 1.0 equiv of the yne allyl alcohol **1**, 0.044 equiv of $[Ir(COD)Cl]_2$, (0.2 M in THF).
[b] Yields refer to isolated yields of compounds **2** after flash chromatography on dry silica gel.
[c] Starting from the *trans*-configured yne allyl alcohol.

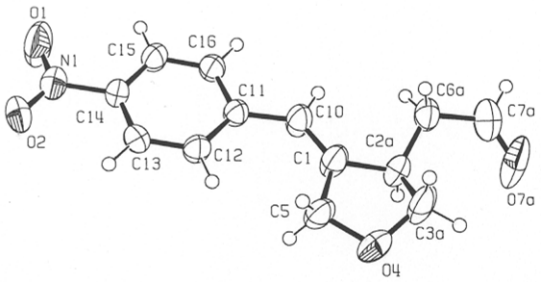
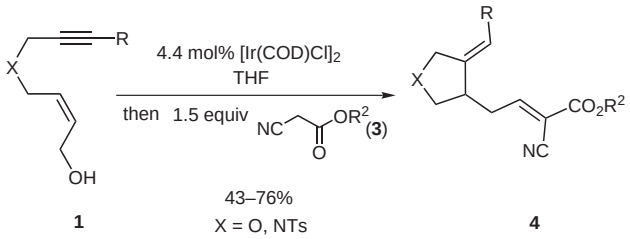


Figure 1 Molecular structure of **2c** (most hydrogen atoms have been omitted for clarity)

With an Ir-catalyzed AEC in hand the stage is set for performing a second Ir-catalyzed step in a sequential fashion. As the reaction medium is literally neutral we chose a sequential combination of AEC and Murahashi reaction,[7] eventually both are iridium-catalyzed processes. Therefore, after reacting the yne allyl alcohols **1** in the presence of $[Ir(COD)Cl]_2$ in THF for 24 hours a slight excess of cyano acetates **3** was added to give after another 24 hours cycloisomerization–condensation products in moderate to good yields (Scheme 3, Table 2).[8,12]



Scheme 3 Ir-catalyzed cycloisomerization–Murahashi sequence

The structures of the sequence products were unambiguously assigned by spectroscopic analyses and, in addition, by an X-ray crystal structure analysis of the pyrrolidine **4e** (Figure 2).[11]

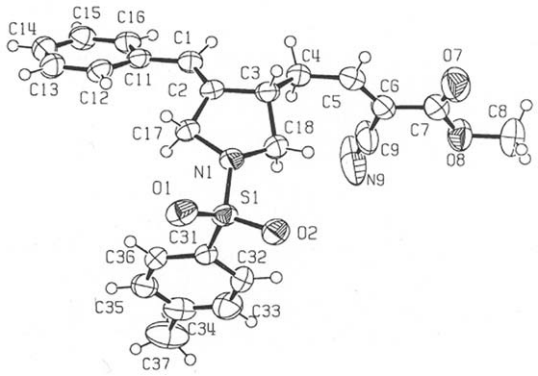


Figure 2 Molecular structure of **4e** (most hydrogen atoms have been omitted for clarity)

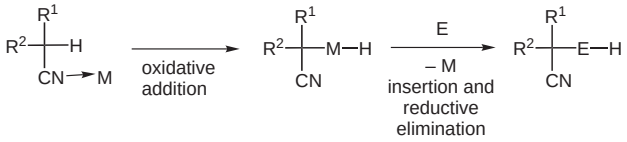
The aldol condensation takes place as a purely iridium-catalyzed process without addition of further bases or acids. Indeed, the iridium catalyst is still active after the initial AEC to catalyze a sequential Knoevenagel-type condensation reaction. By coordination of the metal to the nitrile the basicity of the metal and the acidity of the C–H bond are concomitantly increased and the oxidative addition is simplified (Scheme 4).[7] Thus, the metal–hydrido complex can insert an electrophile, in this case an aldehyde that was formed in the previous AEC. Finally, reductive elimination regenerates the catalytic active species. Besides water, no further by-products are produced.

Remarkably, in most cases room temperature is just sufficient or even necessary to obtain better yields (Table 2, entries 7 and 8). Due to the sensitivity of aliphatic alde-

Table 2 Alder-Ene Cycloisomerization–Murahashi Condensation Sequence Products **3**[a]

Entry	**1**	X	R^1	R^2	Temp (°C)	Product **4**	Yield (%)[b]
1	**1a**	O	Ph	Me	60	**4a**	74
2	**1a**	O	Ph	Me	r.t.	**4a**	73
3	**1b**	O	4-$MeOC_6H_4$	Me	60	**4b**	61
4	**1b**	O	4-$MeOC_6H_4$	Me	r.t.	**4b**	69
5	**1c**	O	4-$O_2NC_6H_4$	Me	r.t.	**4c**	43
6	**1d**	O	4-MeC_6H_4	Me	r.t.	**4c**	70
7	**1e**	TsN	Ph	Me	60	**4e**	17
8	**1e**	TsN	Ph	Me	r.t.	**4e**	72
9	**1b**	O	4-$MeOC_6H_4$	furfuryl	r.t.	**4f**	50
10	**1d**	O	4-MeC_6H_4	furfuryl	r.t.	**4g**	76

[a] Reaction conditions: 1.0 equiv of the yne allyl alcohol **1**, 0.044 equiv of $[Ir(COD)Cl]_2$, (0.2 M in THF). After 24 h addition of 1.5 equiv of the cyano acetate **3**.
[b] Yields refer to isolated yield of compounds **4** after flash chromatography on silica gel.



Scheme 4 Mechanistic rationale by Murahashi

hydes, some of the yields of the products **4** are even higher than for the corresponding AEC step itself (Table 2, entries 1, 2, and 4).

In conclusion, based upon the iridium-catalyzed cycloisomerization of yne allyl alcohols we have developed a novel one-pot Alder–ene cycloisomerization–Murahashi sequence that excels in its simplicity and diversity potential. Studies addressing scope and limitation of this novel sequence are currently underway.

Acknowledgment

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References and Notes

(1) New address: Lehrstuhl für Organische Chemie, Institut für Organische Chemie und Makromolekulare Chemie der Heinrich-Heine-Universität Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany
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(9) All compounds have been fully characterized by spectroscopic methods and by correct elemental analysis or HRMS.

(10) **Typical Procedure of Compound 2c (Table 1, Entry 6).** To a solution of 30 mg (44 μmol) of $[IR(COD)Cl]_2$ in 5 mL of anhyd THF were added 252 mg (1.02 mmol) of **1c**. The reaction mixture was stirred at 60 °C for 24 h before it was diluted with Et_2O. After quick chromatography on dry silica gel, 179 mg (71%) of **2c** were obtained as a yellow solid; mp 61–66 °C. R_f = 0.40 (*n*-hexane–Et_2O = 10:90, SiO_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.79 (dd, *J* = 8.4, 18.4 Hz, 1 H), 2.91 (dd, *J* = 5.1, 18.4 Hz, 1 H), 3.42 (m, 1 H), 3.61 (dd, *J* = 5.6, 8.8 Hz, 1 H), 4.16 (dd, *J* = 6.7, 8.8 Hz, 1 H), 4.66 (s, 2 H), 6.46 (s, 1 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 8.20 (d, *J* = 8.8 Hz, 2 H), 9.88 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.8 (CH), 47.3 (CH_2), 69.9 (CH_2), 72.4 (CH_2), 119.8 (CH), 123.9 (CH), 128.4 (CH), 143.2 (C_{quat}), 146.1 (C_{quat}), 149.3 (C_{quat}), 199.9 (CH). MS (EI, 70 eV): *m/z* (%) = 247 (24) $[M]^+$, 230 (38) $[M – OH]^+$, 229 (33) $[M – H_2O]^+$, 204 (31) $[M – C_2H_3O]^+$, 203 (64) $[M – C_2H_4O]^+$, 158 (22) $[M – C_4H_{10}O]^+$. HRMS (EI): *m/z* calcd: 247.0845; found: 247.0822. Anal. Calcd for $C_{13}H_{13}O_4N$ (247.3): C, 63.15; H, 5.30; N 5.66. Found: C, 62.99; H, 5.39; N, 5.52.

(11) CCDC-630817 (**2c**) and CCDC-630818 (**4e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk].

(12) **Typical Procedure for 4e (Table 2, Entry 8).** To a solution of 30 mg (44 μmol) of $[IR(COD)Cl]_2$ in 2.5 mL of anhyd THF were added 360 mg (1.01 mmol) of **1e**. The reaction mixture was stirred at r.t. for 24 h. Then 150 mg (1.51 mmol) of cyanoacetate were added and the reaction mixture was stirred for another 24 h at r.t. After dilution with Et_2O the crude product was chromatographed on silica gel to give 319 mg (0.73 mmol, 72%) of **4e** as a white crystalline solid; mp 166–166.5 °C. R_f = 0.37 (*n*-hexane–Et_2O = 10:90, SiO_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 2.72 (m, 1 H), 2.85 (ddd, *J* = 6.1, 7.7, 13.9 Hz, 1 H), 2.99–3.11 (m, 2 H), 3.41 (ddd, *J* = 2.2, 8.2, 8.3 Hz, 1 H), 3.87 (s, 3 H), 4.23–4.05 (m, 2 H), 6.31 (s, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.43–7.21 (m, 5 H), 7.63 (dd, *J* = 7.9 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 35.1 (CH_2), 43.4 (CH), 50.3 (CH_2), 51.6 (CH_2), 53.3 (CH_3), 111.4 (C_{quat}), 113.3 (C_{quat}), 124.8 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.7 (CH), 129.9 (CH), 132.5 (C_{quat}), 135.7 (C_{quat}), 137.6 (C_{quat}), 144.0 (C_{quat}), 159.4 (CH), 161.2 ($C_{quat.}$). MS (EI, 70 eV): *m/z* (%) = 436 (18) $[M]^+$, 312 (54) $[M – C_6H_6NO_2]^+$, 282 (25) $[M – C_7H_6O_2S]^+$, 281 (100) $[M – C_7H_7O_2S]^+$, 157 (25), 149 (25), 156 (60) $[C_{11}H_{10}N]^+$, 91 (35) $[C_7H_7]^+$. Anal. Calcd for $C_{24}H_{24}O_4N_2S$ (436.5): C, 66.04; H, 5.54; N, 6.42. Found: C, 65.95; H, 5.66; N, 6.35.