Synthetic Methods

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Enantioselective Modular Synthesis of 2,4-Disubstituted Cyclopentenones by Iridium-Catalyzed Allylic Alkylation**

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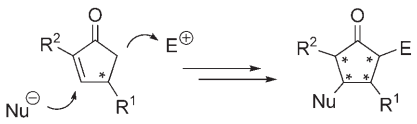
Cyclopentenones are important structural motifs of natural products and pharmaceuticals.[1] Their stereoselective synthesis remains a challenge because of the numerous possible substitution patterns.[2] Here we report a new enantioselective method for the synthesis of 2,4-disubstituted cyclopentenones and its application in the synthesis of some interesting targets. Cyclopentenones are also of interest as intermediates, because of their suitability for reactions at position 3 with nucleophiles and at position 5 with electrophiles; thus, numerous further functionalizations are possible (Scheme 1).[3]



Scheme 1.

The new method is based on the following concept (Scheme 2): a) Iridium-catalyzed allylic alkylation using the enolate of amide **1**, a new prenucleophile, leads to a new chirality center having an adjacent vinyl group with high enantioselectivity.[4] b) The Weinreb-type[5] amide group allows facile conversion of the alkylation product into an enone. c) Finally, the enone can be cyclized by Ru-catalyzed ring-closing metathesis (RCM).[6] The combination of metal-catalyzed allylic alkylation and ring-closing metathesis is already known as a method for the construction of cyclic compounds;[4f,7] however, it has not yet found broad application in organic synthesis.

Over the last few years iridium-catalyzed allylic alkylation has evolved into a reliable method for enantioselective C–C bond formation.[4] The phosphorus amidite ligands, introduced by Alexakis and Feringa,[4g,8] have proved to be

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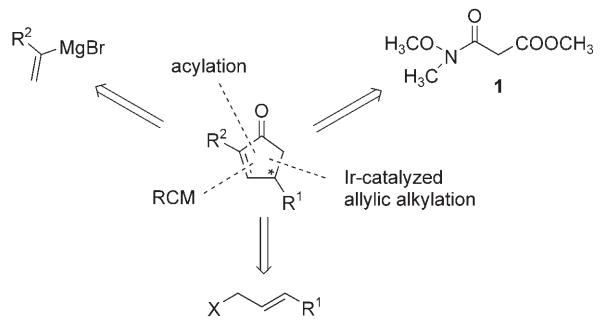
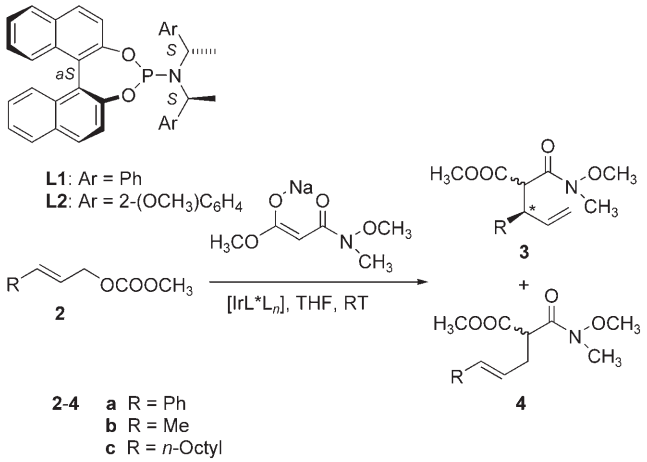


Scheme 2. Retrosynthetic concept.

particularly well suited for these reactions. Catalysts prepared by reaction of [{Ir(cod)Cl}$_2$] (cod = cyclooctadiene) with **L1** or **L2** and base (Scheme 3) induce very high activity and



Scheme 3. Allylic substitution using a malonic amide of the Weinreb-type derived from dimethyl malonate.

selectivity (see Experimental Section). In these reactions, iridacycles are formed by C–H activation.[4d,9] We applied this method to study allylic alkylations with the enolate of compound **1** as a new nucleophile (Scheme 3). Absolute configurations of the products were assigned in analogy to the results of previously investigated substitutions with malonates and amides as nucleophiles. To date, the steric course of all substitutions yielding a product with known absolute configuration was found to be independent of the nucleophile.[10]

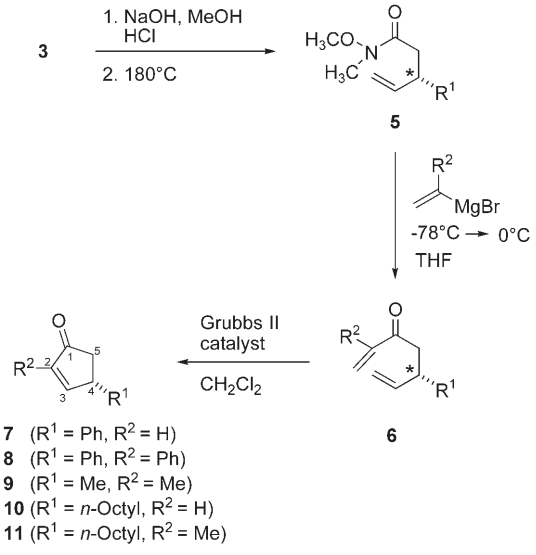
The results displayed in Table 1 demonstrate that the alkylations were fast as well as highly regio- and enantioselective. The enolate of **1** shows reactivity and selectivity similar to that of enolates of malonic esters, which are the standard nucleophiles employed in allylic alkylations. Products **3** were formed as 1:1 mixtures of diastereoisomers, which were neither separated nor characterized because of facile equilibration through enolization of the malonic amide part of the molecule. Enantiomeric excesses were found to be in the range of 95–99% *ee* and regioselectivities, in the range of **3**/**4** = 83:17 to 98:2.

The mixtures of the substitution products **3** and **4** could be smoothly converted in three steps into the corresponding 2,4-disubstituted cyclopentenones in overall yields of >50% (Scheme 4, Table 2). Saponification/decarboxylation gave the amides **5**, and in the next step, reaction with Grignard reagents, the enones **6** were obtained with various substituents in position 2. Subsequent ring-closing metathesis using Grubbs' second-generation catalyst[11] afforded cyclopentenones **7**–**11** (Table 2); side products formed from regioisomers **4** could be separated off easily. The enantiomeric excesses of compounds **3** and those of the corresponding cyclopentenones were identical to within the accuracy of measurement; in other words, the ring-closing metathesis proceeds without

Table 1: Iridium-catalyzed allylic alkylation of carbonates **2a**–**c** according to Scheme 3 (cf. Experimental Section).

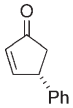
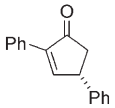
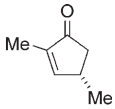
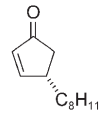
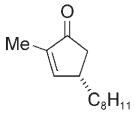
Entry	Substr.	L*	t[a] [h]	Yield **3**+**4** [%][b]	**3**/**4**[c]	*ee* (**3**) [%][d] (abs. config.)
1	**2a**	**L1**	1	89	>98:2	96 (*R*)
2[e]	**2a**	**L2**	0.5	88	>98:2	98 (*R*)
3[e]	**2b**[f]	**L1**	3	83	94:6	95 (*R*)
4	**2b**[f]	**L2**	2	76	94:6	95 (*R*)
5	**2c**[f]	**L1**	18	89	83:17	96 (*R*)
6[e]	**2c**[f]	**L2**	5.5	62	84:16	99 (*R*)

[a] Reaction time. [b] Yield of the isolated mixture of the regioisomeric products **3** and **4**. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral column (Daicel Chiralcel AD-H, 250×4.6 mm, 5 μm with guard cartridge AD-H, 10×4 mm, 5 μm, 0.5 mL min^{-1}). In all cases the branched compounds **3** were obtained as 1:1 mixtures of diastereoisomers; therefore, in each case the chromatograms displayed four peaks. All given absolute configurations refer to the starred chirality center in Scheme 3. Compounds **4** were racemic. Chromatographic conditions and results (*n*-hexane/isopropyl alcohol 95:5, 20°C, 210 nm): t_R[(*S*)-**3a**] = 28 min/37 min, t_R[(*R*)-**3a**] = 33 min/47 min, t_R[**4a**] = 39 min/42 min; (*n*-hexane/isopropyl alcohol 99:1, 20°C, 210 nm): t_R[(*R*)-**3b**] = 36 min/43 min, t_R[(*S*)-**3b**] = 41 min/47 min, t_R[**4b**] = 58 min/64 min; (*n*-hexane/isopropyl alcohol 99:1, 20°C, 220 nm): t_R[(*R*)-**3c**] = 26 min/28 min, t_R[(*S*)-**3c**] = 27 min/32 min, t_R[**4c**] = 31 min/32 min. [e] Reaction was conducted with 0.02 equiv of the Iridium catalyst. [f] The substrate contained 2–3% of the *cis* diastereoisomer.



Scheme 4. Synthesis of chiral cyclopentenones.

Table 2: Synthesis of cyclopentenones according to Scheme 4.

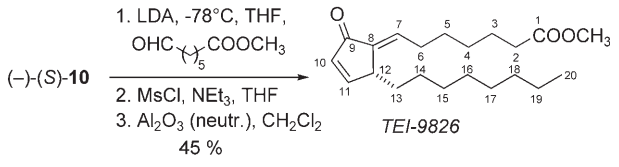
Entry	Substr.	R^1	R^2	Yield [%][a]	Product	*ee* [%][b]
1	(*R*)-**3a**	Ph	H	66	 (–)-(*S*)-**7**	97
2	(*R*)-**3a**	Ph	Ph	55	 (–)-(*S*)-**8**	96
3	(*R*)-**3b**	Me	Me	44[c]	 (–)-(*S*)-**9**	95
4	(*R*)-**3c**	*n*-Octyl	H	56	 (–)-(*S*)-**10**	96
5	(*R*)-**3c**	*n*-Octyl	Me	56	 (–)-(*S*)-**11**	n.d.

[a] Starting from **3** + **4**. [b] Determined by HPLC on a chiral column; in each case synthesis of both enantiomers. [c] Volatile substance.

racemization. With respect to R^2, there is the limitation that with sterically demanding substituents, such as $Si(CH_3)_3$, the ring closure by metathesis is currently not possible.

Of the examples presented in Table 2, compounds **9** and **10** deserve special comment. Enone **9** has been identified as a volatile flavor component of dried fish.[12] A synthesis of the nonracemic compound has not yet been described to the best of our knowledge.

Compound **10** (entry 4 in Table 2) is a particularly interesting target in the area of synthesis of biologically active compounds as it offers a fast access to the prostaglandin analogue *TEI-9826*, a 5-alkylidene-4-alkyl-2-cyclopentenone that displays high anticancer activity against cisplatin-resistant tumors (Scheme 5).[13] Enone **10** has already been synthesized as a racemate and as an enantiomerically pure compound starting from (*S*)-but-3-yn-2-ol (> 98% *ee*), which was obtained by resolution.[14] In our synthesis, the mixture of the regioisomers **3c**/**4c**, which was obtained by allylic alkylation (Table 1, entry 3), was transformed directly into cyclopentenone **10** (cf. Scheme 4). This was obtained in 56% overall yield with an enantiomeric purity of 96% *ee*. The



Scheme 5. Synthesis of *TEI-9826* from (–)-(*S*)-**10**. LDA = lithium diisopropylamide, Ms = methanesulfonyl.

subsequent aldol condensation was carried out according to a procedure described by Kobayashi et al.[2d] and yielded the desired prostaglandin analogue *TEI-9826* with 95% *ee* (Scheme 5).

Finally, we want to direct attention to the chiral 2-substituted cyclopentenones listed in Table 2. In prostaglandin and carbonucleoside chemistry these compounds are of interest as intermediates for the synthesis of analogues.[15]

Experimental Section

General procedure for the iridium-catalyzed allylic alkylation: A solution of the nucleophile was prepared by the dropwise addition of malonic amide **1** (1.3 mmol) to a suspension of NaH (1.3 mmol) in anhydrous THF (4.0 mL) (solution A).

Under an argon atmosphere, a solution of $[\{Ir(cod)Cl\}_2]$ (13.4 mg, 0.02 mmol) and **L1** or **L2** (0.04 mmol) in anhydrous THF (1.0 mL, content of water $< 50\ \mu g\,mL^{-1}$, Karl Fischer titration) was treated with tetrahydrothiophene (18 μL, 0.20 mmol) and 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD, 11.1 mg, 0.08 mmol), and the mixture was stirred for 2 h. Then substrate **2** (1.0 mmol), CuI (38 mg, 0.20 mmol), and solution A were added, and the mixture was stirred for the time given in Table 1; conversion was monitored by thin-layer chromatography. After complete conversion had been reached, Et_2O (5 mL) and saturated NH_4Cl solution (5 mL) were added, and the aqueous phase was extracted with Et_2O (2×20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was analyzed with respect to the ratio **3**/**4** by ^1H NMR spectroscopy and then subjected to flash column chromatography (silica, petroleum ether/ethyl acetate).

Physical data of selected compounds: **10**: $[\alpha]_D^{24} = -129$ ($c = 0.50$, $CHCl_3$) (96% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.5$ Hz, 3H, CH_3), 1.19–1.44 (m, 13H, $CH_{2(n\text{-octyl})}$), 1.45–1.68 (m, 1H, $CH_{2(n\text{-octyl})}$), 1.99 (dd, $^2J_{5a,5b} = 18.8$, $^3J_{5a,4} = 2.1$ Hz, 1H, 5-H_a), 2.52 (dd, $^2J_{5b,5a} = 18.8$, $^3J_{5b,4} = 6.3$ Hz, 1H, 5-H_b), 2.86–2.96 (m, 1H, 4-H), 6.13 (dd, $^3J_{2,3} = 5.7$, $J = 2.0$ Hz, 1H, CH=), 7.63 ppm (dd $^3J_{3,2} = 5.6$, $J = 2.4$ Hz, 1H, CH=); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.22$ (q, CH_3), 22.78, 27.75, 29.36, 29.58, 29.73, 31.97, 34.89 (7 t, $CH_{2(n\text{-octyl})}$), 41.20 (t, C-5), 41.63 (d, C-4), 133.68, 168.82 (2 d, C-2, C-3), 210.23 ppm (s, C-1).

TEI-9826: $[\alpha]_D^{20} = -121$ ($c = 0.58$, $CHCl_3$) (95% *ee*); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J_{20,19} = 7.1$ Hz, 3H, 20-H), 1.18–1.33 (m, 12H, CH_2), 1.34–1.42 (m, 2H, CH_2), 1.45–1.55 (m, 3H, CH_2), 1.58–1.68 (m, 2H, CH_2), 1.75–1.85 (m, 1H, CH_2), 2.18–2.32 (m, 4H, 2-H, 6-H), 3.46 (m, 1H, 12-H), 3.66 (s, 3H, OCH_3), 6.32 (dd, $^3J_{10,11} = 6.0$, $^4J_{10,12} = 2.0$ Hz, 1H, 10-H), 6.51 (t, $^3J_{7,6} = 7.8$ Hz, 1H, 7-H), 7.53 ppm (dd, $^3J_{11,10} = 6.0$, $^3J_{11,12} = 2.0$ Hz, 1H, 11-H); ^{13}C NMR (125 MHz, $CDCl_3$): 14.22 (q, C-20), 22.77, 24.86, 26.01, 28.48, 29.04, 29.05, 29.36, 29.58, 29.91, 31.97, 32.61, 34.04 (12 t, C-2, C-3, C-4, C-5, C-6, C-13, C-14, C-15, C-16, C-17, C-18, C-19), 43.46 (d, C-12), 51.63 (q, OCH_3), 134.92 (d, C-10), 135.33 (d, C-7), 138.25 (s, C-8), 162.12 (d, C-11), 174.17, 197.11 ppm (2s, C-1, C-9).

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