Chromium(0)-Promoted $[6\pi + 2\pi]$ Cycloadditions of Allenes with Cycloheptatriene

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Photoinitiated $[6\pi + 2\pi]$ cycloadditions of allenes with (η^6 -cycloheptatriene)tricarbonylchromium(0) (1) are described. An example of asymmetric induction obtained by reaction of 1 with a chiral 1,3-disubstituted allene is also reported.

Transition-metal-mediated higher-order cycloaddition reactions have become important synthetic tools for the construction of medium-sized ring targets.¹ In particular, Cr(0)promoted $[6\pi + 4\pi]$ and $[6\pi + 2\pi]$ cycloadditions with cyclic trienes have been extensively studied in the context of synthetic applications.^{2,3} These transformations can be initiated either photochemically or thermally; however, photochemical activation appears to be more compatible with sensitive reaction partners. Thus, isocyanates and ketenes have been successfully used as 2π partners in the photoinduced $[6\pi + 2\pi]$ cycloaddition reactions with (cycloheptatriene)tricarbonylchromium(0) (1), whereas they were less

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best of our knowledge, the metal-mediated $[6\pi + 2\pi]$ cycloaddition of allenes has not been described previously.⁵ Thermal, metal-free cycloadditions of allenes to cyclic trienes such as tropone and azaheptafulvenes have been studied, but

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Table 1. Photoinitiated $[6\pi + 2\pi]$ Cycloaddition Reaction of 1 with 1,1-Disubstituted Allenes 2a-c



^{*a*} Procedure A: a mixture of **1** (1 equiv) and allene (2 equiv) in hexanes was irradiated at rt in a pyrex tube for periods of 4-6 h. Procedure B: to a solution of **1** in hexanes in a pyrex tube was introduced under irradiation at rt slowly a solution of allene (2 equiv) in hexanes via a syringe pump, then additional irradiation was continued for 4-6 h. See Supporting Information for more details. ^{*b*} Yield of isolated product after purification by flash chromatography.

only $[8 + 2]^6$ or $[4 + 2]^7$ cycloadducts were isolated depending on the nature of the allene.

Herein, results of a study on the photoinitiated $[6\pi + 2\pi]$ cycloaddition of allenes with (η^6 -cycloheptatriene)tricarbo-nylchromium(0) (1) are reported.

All of the following cycloaddition reactions were performed in a pyrex reactor with a 450 W Canrad-Hanovia medium pressure Hg vapor lamp. Two different procedures were evaluated in the study: (a) a mixture of complex 1 (1) equiv) and allene (2 equiv) in hexanes was directly irradiated (procedure A); (b) a solution of allene (2 equiv) in hexanes was added slowly to a solution of 1 in hexanes using a syringe pump under continuous irradiation (procedure B). A preliminary experiment was performed with complex 1 and 1,1-diphenyl-1,2-propadiene (2a) following procedure A. The metal-free [6 + 2]-cycloadduct **3a** was obtained in 50% yield as a single regioisomer (Table 1, entry 1). Similar results were observed with vinylidenecyclohexane (2b) and trisubstituted allene 2c using procedure B, affording cycloadducts 3b and 3c, respectively, in moderate yields (entries 2 and 3). In each case, cycloaddition occurred at the less sterically congested double bond of the 2π partner. Regioisomer 3c was isolated as a single diastereomer resulting from an exclusive endo approach of the allene, paralleling the $[6\pi + 2\pi]$ cycloaddition with alkenes.^{8,9}

1,3-Disubstituted allenes were then examined. When allene **4a** was employed using procedure A, a single isomer **5a** was obtained in 59% yield (Table 2, entry 1). The addition occurred exclusively at the unsaturation bearing the CH₂OTBS substituent via an endo transition state. The phenyl group on the exocyclic double bond in **5a** was found to be

Table 2. Photoinitiated $[6\pi + 2\pi]$ Cycloaddition Reaction of 1 with 1,3-Disubstituted Allenes $4\mathbf{a}-\mathbf{c}$



				vield	isomeric ratio c	
entry	allene	$procedure^a$	product	$(\%)^b$	5 (<i>E</i> / <i>Z</i>)	6 (E/Z)
1	4a	А	5a	59	100 (>99:<1)	0
2	4a	В	5a	50	$100 (85:15^d)$	0
3	4b	А	$\mathbf{5b}^{e}$	56^{f}	100 (>99:<1)	0
4	4 c	В	5c, 6c	64	88 (10:90)	12(23:77)

^{*a*} See footnote *a* of Table 1. ^{*b*} Overall yield (5 + 6) of isolated product after purification. ^{*c*} Ratios (5/6, *E/Z*) determined by GC analysis on the crude product before purification. ^{*d*} Sometimes $E/Z \sim 98:2$. ^{*e*} Isolated as an alcohol after removal of the THP group. ^{*f*} Yield over two steps after removal of the THP group.

syn coplanar with the (C-8)-(C-1) bond and, consequently, orientated away from the substituent at C-7.10 Subsequent X-ray crystallographic analysis performed on a derivative of 5a (p-nitrobenzoate ester) confirmed the structural and stereochemical assignments (see Supporting Information). Surprisingly, when the same cycloaddition was performed using the "slow addition" technique (procedure B), the Z isomer of 5a with the phenyl group syn to C-7 could also be detected (E/Z = 85:15, entry 2). In rare cases, procedure B led to the virtually exclusive formation of the E isomer. For the moment, it is not evident how the rate of slow addition of allene promotes the formation of the Z isomer. The cycloaddition with 4b (procedure A) behaved similarly to the cycloaddition with 4a to give, after deprotection of the THP group, uniquely the alcohol (E)-endo-5b (56% over two steps, entry 3). Irradiation of 1 with 4c (procedure B) gave a 88:12 mixture of regioisomers endo-5c and endo-6c in 64% overall yield (entry 4). Curiously, cycloaddition also occurred at the π bond bearing the phenyl group. The high regioselectivity observed when an ether group was present is consistent with a prior coordination of the oxygen atom to the chromium center which should favor bond formation at the π bond bearing the ether substituent. With a methyl group, no coordination is possible, and the steric effects with 1 would be expected to control regioselectivity. Each of the regioisomers 5c and 6c was in turn isolated as a mixture of Z and E isomers. For 5c, the Z isomer with the phenyl group orientated away from the methyl group at C-7 was found to be the major isomer in line with previous results (Table 2, entries 1-3), whereas for the major isomer of **6c**, the methyl group was found to be syn to the phenyl group at C-7.

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⁽⁹⁾ When concerned, the relative configuration of the stereocenter at the C-7 position was established by ¹H NMR NOE difference experiments, and in each case studied, only the *endo*-cycloadduct was obtained. See Supporting Information for additional discussion of structural assignments.

⁽¹⁰⁾ All the *E* and *Z* geometries discussed in this study were supported by ¹H NMR NOE correlations. See Supporting Information for some discussed examples.

Table 3. Photoinitiated $[6\pi + 2\pi]$ Cycloaddition Reaction of 1 with Monosubstituted Allenes 7a-i



^{*a*} See footnote *a* of Table 1. ^{*b*} Overall yield ($\mathbf{8} + \mathbf{9}$) of isolated product after flash chromatography. ^{*c*} Ratios ($\mathbf{8}/\mathbf{9}$, *Z/E*) determined by GC analysis on the crude product before purification or by ¹H NMR. ^{*d*} Adduct **10** (ca. 4% yield) was also formed. ^{*e*} 5 equiv of allene was used. ^{*f*} Isolated as an alcohol after removal of the THP group. ^{*s*} Overall yield over two steps after removal of the THP group. ^{*h*} Tetracycle **11** (5–8% yield) was also isolated. ^{*i*} The reaction mixture was cooled at 0 °C during irradiation, and additional irradiation was continued for 1 h after addition of allene.

Attention was then directed toward cycloaddition of 1 with monosubstituted allenes (Table 3). Preliminary experiments were carried out with any allenes 7a-d bearing various substituents on the phenyl ring. Whenever an arylallene was used, the cycloaddition (procedure B) afforded the 8-type regioisomer with excellent selectivity (ratios 8a-d/9a-d >97:3 by GC analysis of the crude mixtures) and with moderate yields (entries 1-4). Each regioisomer was isolated as an inseparable mixture of Z and E isomers in ratios of 50:50. In contrast to the case with 1,3-disubstituted allenes, the absence of a substituent at the C-7 position in the final products would reduce steric interactions and would allow the aryl substituent to be placed syn to C-7 more easily. When a mixture of 1 and ethyl buta-2,3-dienoate (7e) was irradiated, the cycloaddition occurred only at the terminal double bond of the allene to afford the regioisomer 8e as a separable 65: 35 mixture of Z and E isomers in 34% yield (entry 5). No addition to the electron-deficient double bond of the allene was observed. This result is in stark contrast to that obtained in the $[6\pi + 2\pi]$ cycloaddition with alkenes in which only electron-deficient alkenes participate in the cycloaddition process.^{8a} It is also noteworthy that **8e** isomerizes during the reaction to give 10 (ca. 4%). The yield of 8e could be dramatically improved by using 5 equiv of allene instead of the usual 2 equiv (entry 6). Irradiation of 1 with protected buta-2,3-dienol (7f) (procedure A or B) yielded a separable 40:60 mixture of regioisomers 8f and endo-9f in 38% overall yield (entry 7). In contrast to the cycloadditions with arylallenes or allenic ester 7e, there was a slight preference for reaction at the internal double bond of the allene. This might be explained by a prior coordination of the oxygen atom of the ether group to the metal center, which would favor attack at the substituted double bond. A similar behavior was observed when 7g was examined (entry 8). Cycloaddition of 1 with methoxyallene (7h) (procedure B) took place preferentially at the internal and electron-rich double bond of the allene, to give a 25:75 mixture of 8h and endo-9h in a 51% overall yield (entry 9). When the bulkier alkoxyallene 7i was engaged, the regioselectivity of the cycloaddition was found to reverse relative to the cycloaddition with 7h, giving mixtures of 8i and endo-9i in 60-65:40-35 ratios (entries 10-12). This reversal might be due to the presence of the bulky TBS group, which would disfavor approach of the allene from the internal double bond. An optimum overall reaction yield of 64% was obtained when reaction was performed at 0 °C using procedure B (entry 12). It is also noteworthy that the Z/E selectivity for 8-type adducts was the same when 1-alkoxypropa-1,2-dienes 7h,i or 4-alkoxybuta-1,2-dienes 7f,g were employed (substituent preferentially syn to C-7), whereas it was reversed when electron-deficient allene 7e was used (substituent preferentially anti to C-7).

In the reactions that gave cycloadducts **8i** and **9i**, a new adduct identified as the tetracyclic **11** was also isolated as a single diastereomer (5–8%, Table 3, entries 10–12). The structure of **11** was unambiguously established by analysis of 1D and 2D NMR data (¹H, ¹³C, Dept, COSY, HMQC, Homodecoupling, INADEQUATE, and NOE sequences). A final confirmation of the structural and stereochemical assignment was provided by an X-ray crystallographic analysis performed on its diol derivative (see Supporting Information). This structure appears to be novel and might arise from a second Cr(0)-mediated [$6\pi + 2\pi$] cycloaddition between cycloadduct **9i** and allene **7i** (Scheme 2). Such a tandem cycloaddition process has precedent in metal-



mediated cycloaddition.¹¹ Work is currently in progress to identify conditions that would favor the formation of this tetracyclic core and to obtain a better understanding of this unusual transformation.

Finally, to evaluate asymmetric induction in the [6 + 2] cycloaddition, a preliminary investigation was performed with a chiral, nonracemic allene.

Chiral propargylic alcohol (*R*)-13 was prepared in 31% yield and $88\% \pm 5\%$ ee¹² via enantioselective addition of terminal alkyne 12 to benzaldehyde using a procedure described by Carreira¹³ (Scheme 3). Compound (*R*)-13 was



then converted to allene (*S*)-**4a** (33%, 60% \pm 5% ee) in a two-step one-pot process.¹⁴ The enantiomeric excess was determined by ¹H NMR using a chiral shift reagent (Ag(fod)-Yb(tfc)₃).¹⁵

Irradiation of 1 with (S)-4a using procedure A afforded cycloadduct (E)-5a (45%). Subsequent removal of the

protecting TBS group gave the optically active alcohol **5b** in $54\% \pm 5\%$ ee,¹² demonstrating a good transfer of the chiral information from the allene (Scheme 4).



In summary, we have validated the first Cr(0)-mediated $[6\pi + 2\pi]$ cycloaddition of allenes with cycloheptatriene under photochemical activation and demonstrated its potential by constructing an enantioenriched bicyclo[4.2.1]nonane framework starting from a chiral allene. Regiochemistry and E/Z selectivity in this cycloaddition were found to be subtly dependent on competing steric and electronic effects of the allene substituents. Further studies of this cycloaddition and investigation of synthetic applications are currently underway.

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Supporting Information Available: Experimental procedures, full characterization data, ¹H and ¹³C NMR spectra for all new compounds, and NOE descriptions and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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