Totally Stereocontrolled Intermolecular Pauson−Khand Reactions of *N*-(2-Alkynoyl) Sultams

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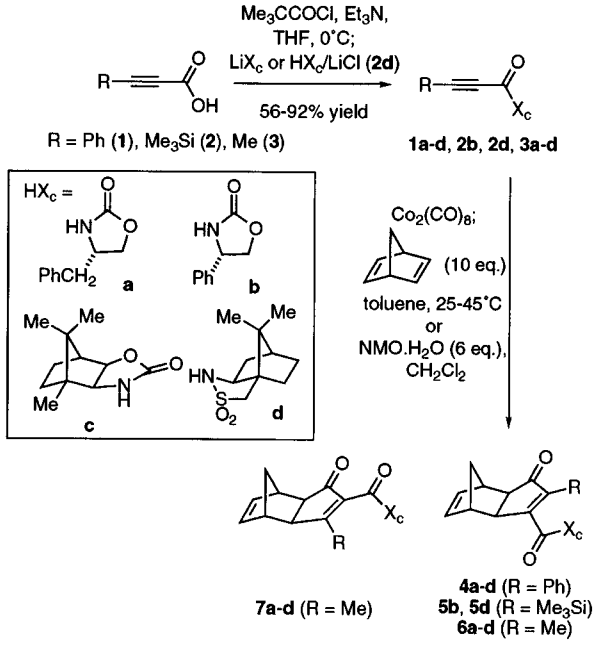
The convergent assembly of cyclopentenones from an alkene and an acetylene−dicobalt hexacarbonyl complex, usually known as the Pauson−Khand reaction, has become a well-established synthetic method.[1] To the ever-increasing use of this process have contributed both recent discoveries of effective promoters of the reaction[2] and the development of catalytic[3] and of asymmetric versions. Two main strategies have been used in enantioselective approaches to the reaction, involving the transfer of chirality either from dicobalt hexacarbonyl complexes possessing a disymmetric C_2Co_2 core[4] or from removable chiral auxiliaries attached to the cyclization components.[5] Only very recently the first examples of an enantioselective catalytic intramolecular Pauson−Khand type process based on chiral titanocene complexes have been disclosed.[6] In the past few years, we have shown that good levels of diastereoselectivity can be attained in the intramolecular Pauson−Khand reactions of enol ethers[5a] or alkoxyacetylenes[5b] derived from chiral alcohols and that the resulting cycloadducts can be applied to the enantioselective synthesis of natural products.[5a,e,f] In the extension of this approach to intermolecular Pauson−Khand reactions, the best results to date involve the use of the alkoxyethyne−dicobalt hexacarbonyl complex derived from 10-(methylthio)isoborneol, which can be converted to an unstable, sulfur-chelated dicobalt pentacarbonyl complex whose low-temperature reaction with norbornadiene takes place with 92% diastereomeric excess (de).[5c] In the absence of chelation effects, however, intermolecular cyclizations of chiral alkoxyacetylenes are much less stereoselective.[5d] *Herein, we report that exceptionally high levels of regio- and stereoselectivity can be easily achieved by pure steric control and under standard reaction conditions in the intermolecular Pauson−Khand reaction of N-(2-alkynoyl) derivatives of chiral oxazolidinones and sultams, especially for Oppolzer's 10,2-camphorsultam.*

The original impetus for this research came from the observation that for certain chiral alcohols the stereoselectivities

Scheme 1



obtained in the Pauson−Khand reaction of the derived 2-alkynoates are greater than those observed for the corresponding *O*-alkyl ynol ethers, even though in the former derivatives the stereogenic centers of the auxiliary are farther from the acetylene moiety.[7] We reasoned that this could be due to a restricted conformational mobility of the carboxyl group in the dicobalt hexacarbonyl complexes and that one could expect higher degrees of stereoselectivity by replacing the ester linkage by a less-mobile amide bond. To test these ideas, we prepared a series of 2-alkynoyl derivatives of the homochiral 2-oxazolidinones **a**−**c** and of (+)-10,2-camphorsultam (**d**) (Scheme 1). The requisite alkynes (compounds **1**−**3**) could be obtained in good yields by nucleophilic attack of the lithium salt (or lithium chloride complex for **3d**) of the chiral auxiliary on a pivalic-2-alkynoic mixed anhydride.[8] The intermolecular Pauson−Khand cocyclization of these electron-deficient alkynes with norbornadiene[9] was next investigated (Scheme 1). The acetylene−dicobalt hexacarbonyl complexes were readily obtained by treatment of a solution of the alkyne with a slight excess of dicobalt octacarbonyl and, without isolation, were reacted with norbornadiene, using either the classical thermal conditions[1] or chemical activation,[2a,b] to give in all cases the *exo*-adducts (**4**−**7**) in high yield. The reactions of both the phenylpropiolic (**1a**−**d**) and the (trimethylsilyl)propiolic acid derivatives (**2b**,**d**) turned out to be completely regioselective, leading exclusively to the 3-carbamoyl cyclopentenones **4** and **5**, respectively. The reactions of the 2-butynoic acid derivatives **3a**−**d** were much less regioselective, the 1,3-dicarbonylic regioisomers **7a**−**d** also being obtained in substantial amounts and with low stereoselectivity.

The results on the formation of the 3-carbamoyl derivatives **4**−**6** are summarized in Table 1. We first discuss the cyclization of the phenylpropiolyl derivatives **1a**−**d**. In addition to the unusually mild reaction conditions, the high yields, and the complete regioselectivity, the stereoselectivity of the process is remarkable and appears to be extremely sensitive to the

(1) For a recent review on the Pauson−Khand reaction, see: Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Elsevier: Oxford, 1995; Vol. 12, pp 703−739.

(2) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204−206.

(3) (a) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285−2286. (b) Chung, Y. K.; Lee, N. Y. *Tetrahedron Lett.* **1996**, *37*, 3145−3148 and references therein.

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(6) Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688−11689.

(7) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 4239−4254.

(8) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271−2273 and references therein.

(9) For derivatives **1a**−**d** and **3a**−**d**, all of the reactions reported in Table 1 gave essentially the same yields and isomer ratios upon replacement of norbornadiene with norbornene.

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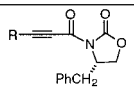
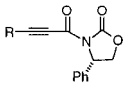
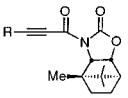
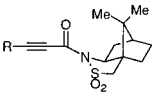
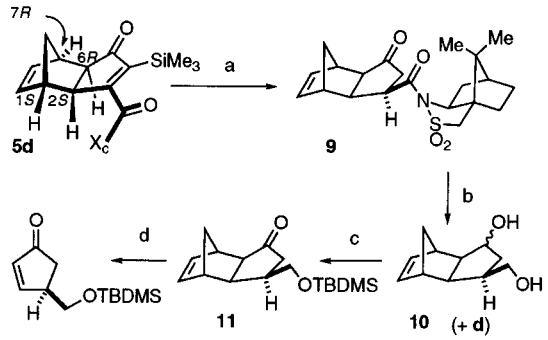
Table 1. 3-Carbamoylcyclopentenones from the Pauson−Khand Reaction of *N*-Alkynoyl Derivatives of Oxazolidinones and Sultams with Norbornadiene

Entry	Starting alkyne	Reaction conditions[a]	Product (yield, d.r.[b])
1		R = Ph (**1a**) A, r.t., 24 h	**4a** (97%, 1:1)
2		R = Me (**3a**) A, r.t., 14 h	**6a** (36%, 2:1)[c]
3		R = Ph (**1b**) A, r.t., 21 h	**4b** (96%, 5.2:1)
4		R = Me_3Si (**2b**) B, 0°C to r.t., 14 h	**5b** (88%, 3.6:1)
5		R = Me (**3b**) A, r.t., 72 h	**6b** (53%, 7.6:1)[d]
6		R = Ph (**1c**) A, r.t., 21 h	**4c** (97%, 14:1)
7		R = Me (**3c**) A, r.t., 96 h	**6c** (34%, 17.5:1)[e]
8		R = Ph (**1d**) A, 45°C, 21 h	**4d**(91%, 523:1)
9		R = Ph (**1d**) B, 0°C to r.t., 1h	**4d**(93%, >800:1)[f]
10		R = Me_3Si (**2d**) B, 0°C to r.t., 18 h	**5d** (78%, >800:1)[f]
11		R = Me (**3d**) A, 45°C, 12 h	**6d** (55%, 318:1)[g]

[a] Conditions: (A) stirring the preformed complex in toluene solution at the specified temperature in the presence of 10 equiv of olefin under nitrogen; (B) chemical activation of the complex by *N*-methylmorpholine *N*-oxide monohydrate in dichloromethane solution. [b] By ^{13}C NMR and HPLC (Nucleosil C-18 column, methanol/water as eluent). [c] In admixture with regioisomer **7a** (44% yield, 1.2:1 dr). [d] In admixture with regioisomer **7b** (23% yield, 1.9:1 dr). [e] In admixture with regioisomer **7c** (38% yield, 5.1:1 dr). [f] HPLC detection limit established using the authentic diastereomer mixture. [g] After chromatographic separation from regioisomer **7d** (24% yield, 1.7:1 dr).

structure of the chiral controller; in effect, whereas the benzyl oxazolidinone **a** (entry 1) leads to an easily separable, equimolar mixture of two diastereomers, the closely related phenyl oxazolidinone **b** (entry 3) produces a *ca*. 5:1 diastereomer mixture, from which the major isomer can be readily isolated in 70% yield by simple column chromatography. Since a substantial increase in the stereoselectivity (up to 14:1; major diastereomer isolated in 90% yield) results from the use of the camphor-derived oxazolidinone **c** (entry 6), it is clear that the steric hindrance at the C-4 position of the oxazolidinone ring can be correlated with the stereochemical outcome of the reaction. The highest levels of stereocontrol are, however, attained in the thermal Pauson−Khand cyclization of the phenylpropynoyl derivative of Oppolzer's bornane-10,2-sultam (**1d**, entry 8), which results in the almost exclusive formation of a single diastereomer (523:1 diastereomer ratio (dr)). When the reaction is run by *N*-oxide activation and under intentionally careless conditions (addition of 6 equiv of the *N*-oxide in a single portion and stirring of the mixture at room temperature in an open vessel), the yield and stereoselectivity are still improved (entry 9). Among the (trimethylsilyl)propynoyl derivatives, **2b** appears to be slightly less selective than **1b** (entry 4); however, the bornane-10,2-sultam derivative **2d** shows again a complete stereochemical control (entry 10). The diastereomer ratios of the 1,4-dicarbonylic regioisomers **6** arising from the 2-butynoyl derivatives **3** follow the trends already observed for the phenyl- and (trimethylsilyl)propiolic amides, the most outstanding result again being that of the bornane-10,2-sultam derivative **6d**, which is formed virtually as a single diastereomer and can be isolated in 55% yield after its chromatographic separation from **7d** (entry 11). It appears therefore that, *independent of the substitution of the alkyne, Oppolzer's bornane-10,2-sultam leads to the totally stereocontrolled formation of the 3-carbamoyl cyclopentenone* and with the 1*S*,2*S*,6*R*,7*R* configuration in the newly created stereogenic centers (Scheme 2).[10]

Scheme 2[a]



[a] Conditions: (a) Zn, 1:1 AcOH/H_2O, rt, 1 h, 62% (19% of epimer); (b) $LiAlH_4$, 4:1 Et_2O/THF, 0 °C, 1 h, 97% (100% of bornane-10,2-sultam); (c) (i) 1.1 equiv of $^tBuMe_2SiCl$, imidazole, DMF, rt, 14 h, 66%; (ii) PDC, DMF, rt, 1 h, 94%; (d) *o*-dichlorobenzene, reflux, 24 h, 63% (29% recovery of **11**).

As an initial illustration of the possible synthetic applications that can be envisaged for these readily obtained, stereopure Pauson−Khand adducts, we outline in Scheme 2 the preparation of 4(*R*)-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-cyclopentenone (**8**). Chemoselective hydrogenation of the cyclopentenone double bond and reductive cleavage of the trimethylsilyl group in **5d** were simultaneously achieved by treatment with activated Zn dust in aqueous acetic acid, to give a mixture of epimers at C-3 from which the major component (**9**) could be isolated in 62% yield by column chromatography. Subsequent reaction of this compound with lithium aluminum hydride produced the diol **10** and bornane-10,2-sultam (**d**), both in essentially quantitative yields; selective protection of the primary hydroxyl and oxidation of the secondary gave access to the tricyclic ketone **11** (62% overall yield), which by heating in *o*-dichlorobenzene[11] underwent the expected retro-Diels−Alder reaction. The 4-substituted cyclopentenone **8** thus obtained (89% selectivity, 71% conversion) showed an enantiomeric purity higher than 96%,[12] indicating that the retrocycloaddition had taken place essentially without racemization.

In summary, the intermolecular Pauson−Khand reaction of 2-alkynoyl derivatives of the widely used chiral auxiliaries 2-oxazolidinones and bornanesultams with norbornadiene or norbornene proceeds in a highly stereocontrolled manner, with excellent yields and under mild and simple experimental conditions. In particular, Oppolzer's bornane-10,2-sultam gives rise to completely stereopure 1,4-dicarbonylic adducts in all of the cases studied. Due to the availability of the starting alkynes and to the variety of conditions for the removal of the chiral auxiliaries, the resulting Pauson−Khand adducts offer considerable interest for the efficient enantioselective construction of chiral synthetic intermediates or ligands.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1a**−**d**, **2b**,**d**, **3a**−**d**, **4a**−**d**, **5b**,**d**, **6a**−**d**, **7a**−**d**, and **8**−**10**; determination of the absolute configuration of adducts **4b**,**d** and **5b**,**d**; determination of the diastereomeric purity of bornanesultam-derived adducts; and rationalization of the stereochemical outcome of the reaction (36 pages). See any current masthead page for ordering and Internet access instructions.

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(10) The absolute configurations of adducts **4b**,**d** and **5b**,**d** were assigned by a combination of chemical correlation, CD spectra, and X-ray crystal structure determination. Complete details will be reported in the full paper.

(11) Takano, S.; Moriya, M.; Ogasawara, K.*Tetrahedron Lett.* **1992**, *33*, 329−332.

(12) By chiral GC (α-DEX column) of the saturated hydroxy ketone derived from **8** by sequential catalytic hydrogenation (10% Pd on C, 1 atm of H_2, CH_2Cl_2, rt, 6 h; 100% yield) and desilylation (tetrabutylammonium fluoride monohydrate, THF, 0 °C, 1 h; 100% yield). It is worth noting that this hydroxy ketone is an advanced synthetic precursor of the antibiotic (+)-sarcomycin.[15]

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