Regio- and Diastereoselective Tandem Rhodium-Catalyzed Allylic Alkylation/ Pauson−Khand Annulation Reactions

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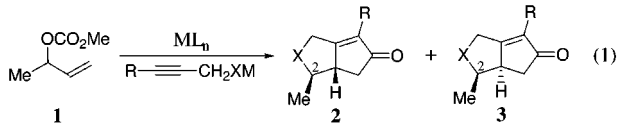
Received January 10, 2001

The construction of complex polycyclic systems using transition metal-catalyzed annulation reactions provides a powerful strategy for target directed synthesis.[1] The Pauson−Khand (PK) annulation is representative of this class of transformations in which a *tethered* eneyne undergoes a formal [2 + 2 + 1] reaction to furnish a bicyclic cyclopentenone.[2,3] A significant limitation with this process is the necessity for *intra*molecularity in order to suppress competitive *inter*molecular metal-catalyzed reactions. However, a recent study provided a new approach to this problem, which utilized a dual catalytic system to facilitate a one-pot palladium-catalyzed allylic alkylation followed by a rhodium-catalyzed PK annulation reaction.[4]

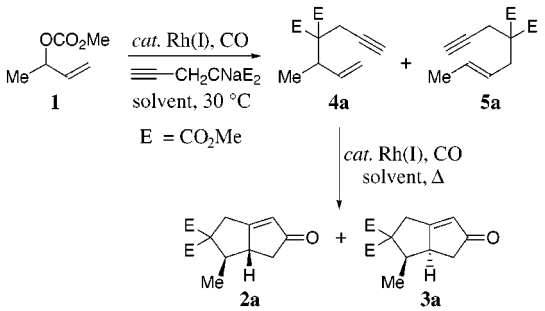
We envisioned an alternative approach to this problem that utilized a single metal-catalyst to facilitate both transformations in a tandem sequence, using *only* the reaction temperature to modulate the catalytic activity. The obvious advantage of this strategy was the ability to significantly increase the molecular complexity of the bicyclic adduct through the introduction of a stereogenic center at C-2, which we anticipated would control diastereoselectivity in the PK annulation.[5] Herein, we now describe the development of the regio- and diastereoselective rhodium-catalyzed *tandem* allylic alkylation/Pauson−Khand annulation reaction using stabilized carbon and heteroatom nucleophiles (eq 1).



(1)

Preliminary studies examined the feasibility of the metal-catalyzed multicomponent annulation reaction (Table 1). We anticipated that the tandem process would evolve from the combination of the rhodium-catalyzed allylic substitution[6] with the PK annulation.[3c,4] Initial efforts with the trimethyl phosphite modified Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) that had proven effective for the allylic substitution reactions[6] furnished only trace amounts of the annulation adducts **2a**/**3a**. Hence, we decided to reexamine the allylic alkylation with rhodium catalysts that had proven effective for the PK reaction. Interestingly, although the PK catalysts were significantly different, we reasoned the strong π-acidity of a carbon monoxide ligand may be sufficient to attain high regioselectivity in the allylic substitution.[6a] Treatment of the allylic carbonate **1** with the sodium salt of the α-branched malonate and $[RhCl(CO)dppp]_2$, in tetrahydrofuran and toluene respectively, furnished alkylation products **4a**/**5a** with ≥12:1 regioselectivity (entries 1−2). The corresponding PK reaction with **4a** furnished the bicyclic adducts **2a**/**3a** with modest diastereoselectivity, favoring the *cis*-adduct **2a**.

Table 1. Development of the Sequential Rhodium-Catalyzed Allylic Alkylation/Pauson−Khand Annulation



entry	catalyst[a]	additive	solvent	2°:1° **4:5**[b,c]	yield (%)[d]	ds **2:3**[e]	yield (%)[d]
1	$[RhCl(CO)dppp]_2$	None	THF	31:1	86	3:1	40
2	"	"	toluene	12:1	47	5:1	80
3	"	AgOTf	THF	16:1	58	5:1	63
4	"	AgOTf	toluene	15:1	59	5:1	35
5	"	None	DMSO	18:1	57	1:1	57
6	"	"	DME	17:1	36	10:1	34
7	"	"	**MeCN**	**37:1**	**88**	**7:1**	**87**
8	$RhCl(CO)(PPh_3)_2$	"	"	3:1	72	3:1	12
9	RhCl(CO)dppe	"	"	8:1	36	4:1	18
10	$[RhCl(CO)dppb]_2$	"	"	8:1	62	5:1	20

[a] All reactions were carried out on a 0.25 mmol reaction scale using 10 mol% rhodium and 1.2 equiv of the propargyllic nucleophile. [b] Ratios of regioisomers were determined by capillary GLC on aliquots of the crude reaction mixture. [c] The primary product **5a** was prepared independently *via* Pd(0) catalysis.[8] [d] GLC yields. [e] Ratios of diastereoisomers were determined by capillary GLC.

Initial efforts to improve catalyst turnover and selectivity, through an *in situ* counterion exchange with AgOTf, resulted in reduced turnover and similar selectivity irrespective of the solvent (entries 3−4). The disparity between the solvents prompted the examination of alternatives that could potentially facilitate both transformations with improved turnover and selectivity. This study provided acetonitrile as the potential medium to facilitate the tandem reaction (entries 5−7). Finally, a series of electronically similar rhodium catalysts, in which the steric environment of phosphine was systematically altered, were examined to determine the optimum catalyst (entries 8−10).

The ability to catalyze both transformations with $[RhCl(CO)dppp]_2$ in acetonitrile, albeit at different reaction temperatures, allowed the development of the tandem process (Table 2). Treatment of the allylic carbonate **1** with the sodium salt of the α-branched dimethyl malonate derivative and $[RhCl(CO)dppp]_2$

† This work was initiated at the Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716.

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10.1021/ja015531h CCC: $20.00
Published on Web 04/19/2001

Table 2. Scope of the Regio- and Diastereoselective Tandem Rhodium-Catalyzed Allylic Alkylation/Pauson−Khand Annulation Reaction (eq 1)[a]

entry	X	M	R	*2°:1°* **4:5**[b]		ds **2:3**[c]	yield (%)[d]
1	$(MeO_2C)_2C$	Na	H	**a**	27:1	5:1	82
2	"	"	Me	**b**	19:1	6:1	80
3	"	"	Ph	**c**	11:1	9:1	78
4	TsN	Li	H	**d**	20:1	3:1	79
5	"	"	Me	**e**	32:1	6:1	84
6	"	"	Ph	**f**	57:1	7:1	81
7	O	Li	H	**g**	5:1	≥19:1	63
8	"	"	Me	**h**	7:1	≥19:1	73
9	"	"	Ph	**i**	8:1	≥19:1	81

[a] All reactions were carried out on a 0.5 mmol reaction scale using 5−6 mol % of $[RhCl(CO)dppp]_2$ and 1.2 equiv. of nucleophile. [b] Ratios of regioisomers were determined by HPLC and capillary GLC. [c] Ratios of diastereoisomers were determined by 400 MHz ^1H NMR. [d] Isolated yields.

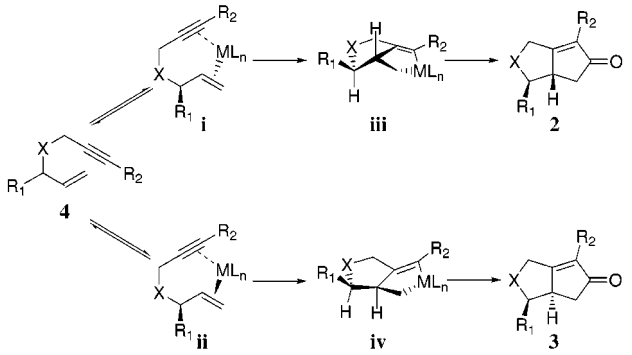
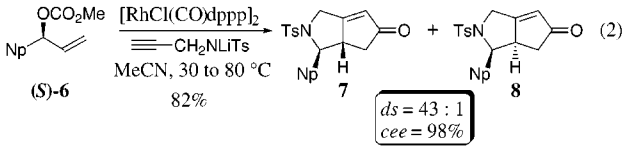


Figure 1.

in acetonitrile at 30 °C, under an atmosphere of carbon monoxide, furnished the enynes **4a/5a** favoring the secondary product **4a** (*2°:1°* = 27:1 by GLC). The reaction mixture was then heated at reflux for ∼24 h, resulting in the formation of the bicyclic cyclopenteneones **2a/3a** in 82% yield, as a 5:1 mixture of diastereoisomers favoring **2a** (entry 1). The relative configuration of the major isomer was established by NMR (nOe), which confirmed the *cis*-relationship of the C-1 bridgehead proton with the C-2 methyl group. *This represents the first regio- and diastereoselective rhodium-catalyzed tandem allylic alkylation/Pauson−Khand annulation reaction.* Table 2 summarizes the application of this method to substituted acetylenic stabilized carbon and heteroatom nucleophiles. This study indicates that the nitrogen nucleophiles provide optimum secondary substitution (TsNRLi > E_2CRNa > ROLi), while the diastereoselectivity, with the exception of the oxygen derivatives **2g**−**i**,[8] is relatively consistent throughout the series.

The diastereoselectivity in the rhodium-catalyzed Pauson−Khand annulation is consistent with the mechanistic hypothesis outlined in Figure 1. Initial complexation of the enyne **4** presumably results in a mixture of diastereomeric complexes (**i/ii**), where the relative population is influenced by the size of the substituent at C-2. Insertion of the metal then leads to the irreversible formation of the diastereomeric metallacycles **iii/iv**, which are poised to undergo migratory insertion of metal bound carbon monoxide, followed by reductive elimination to afford the bicyclic adducts **2/3**. Hence, provided the initial coordination is reversible, increasing the size of the substituent at C-2 should significantly improve the diastereoselectivity.



To test this hypothesis, the C-2 methyl group was replaced with a 2-naphthyl substituent. This study also provided an opportunity to examine the enantiospecificity of the allylic amination with this particular catalyst and thus ascertain whether the allylic substitution was consistent with our previous studies.[6] Treatment of the chiral nonracemic allylic carbonate **(*S*)-6** (≥ 99% *ee*) under the optimized reaction conditions furnished the azabicycles **7/8** in 82% yield, as a 43:1 mixture of diastereoisomers favoring **7** (eq 2).[9] Furthermore, the allylic amination is highly enantiospecific (98% *cee*) and proceeds with retention of absolute configuration.[10]

In conclusion, we have developed a new regio- and diastereoselective tandem rhodium-catalyzed allylic substitution/Pauson-Khand annulation reaction. This study demonstrates that excellent regioselectivity may be obtained with additional rhodium catalysts, provided there is a strong π-acidic ligand present on the metal center. The annulation reaction was also applied to chiral nonracemic allylic carbonate, which is likely to have significant utility for asymmetric synthesis.

Acknowledgment. We sincerely thank the National Institutes of Health (GM58877) for generous financial support. We also thank Zeneca Pharmaceuticals for *an Excellence in Chemistry Award*, Eli Lilly for a *Young Faculty Grantee Award*, GlaxoWellcome for a *Chemistry Scholar Award*, and Novartis Pharmaceuticals for an *Academic Achievement Award*. The Camille and Henry Dreyfus Foundation is also thanked for a *Camille Dreyfus Teacher-Scholar Award* (P.A.E.). Professor Paul A. Wender is acknowledged for stimulating discussions.

Supporting Information Available: Spectral data for **2a**−**i** and **7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The excellent diastereoselectivity observed in this particular series is presumably due to reduced $A^{1,3}$-strain between the C-2 alkyl substituent and ring oxygen (x = 0).

(9) *Representative Experimental Procedure:* Lithium hexamethyldisilyl azide (575 μL, 0.575 mmol, 1.0 M solution in THF) was added dropwise to a solution of *p*-toluenesulfonyl propargylic amine (126 mg, 0.6 mmol) in anhydrous MeCN (3.0 mL) at 30 °C under a CO atmosphere. The anion was allowed to form over *ca.* 20 min, then added *via* Teflon cannula to a solution of $[RhCl(CO)dppp]_2$ (31.4 mg, 0.03 mmol) in anhydrous MeCN (1.0 mL) at 30 °C, rinsing with anhydrous MeCN (2 × 0.5 mL). The optically active allylic carbonate **6** (119 mg, 0.5 mmol; ≥99% *ee* by capillary GLC) was then added from a tared vial and the reaction mixture heated at 30 °C for ∼5 h (TLC control; *2°:1°* ≥99:1 by HPLC). The reaction mixture was heated at reflux under a CO atmosphere for ∼24 h (TLC control). The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (eluting with 60% ethyl acetate/hexane) to furnish the azabicycles **7/8** (0.162 g, 82%) as a white crystalline solid, with 43:1 diastereoselectivity (by crude HPLC analysis) favoring **7** (98% cee).[6b]

(10) The absolute configuration for the rhodium-catalyzed allylic amination was assigned by comparison of **(*S*)-II** prepared from **(*S*)-6** with **(*R*)-II** prepared *via* Mitsunobu inversion of the allylic alcohol **(*S*)-I**.