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Rh(I)-Catalyzed Carbonylative Ring Opening of Diazabicycles with Acyl Anion Equivalents

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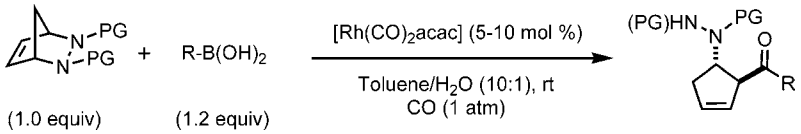
ABSTRACT



A catalytic desymmetrization of strained alkenes by ring-opening of *meso*-diazabicycles with acyl anion nucleophiles is reported. Densely functionalized *trans*-1,2-hydrazinoacyl cyclopentene building blocks are obtained stereoselectively. The acyl anion equivalent is generated in situ under very mild conditions from readily available organoboron precursors.

Acylation reactions are the focus of a growing interest and expand the reaction beyond hydroformylation.[1] The insertion of carbon monoxide into metal−carbon bonds is well precedented with several metals,[2] but rhodium is by far the most versatile in terms of reactivity.[3] In the development of new reactions to desymmetrize meso substrates,[4] the success of rhodium catalysts to effect formal allylic substitutions of activated alkenes[5] prompted us to explore the reactivity of acyl-anion nucleophiles.

The generation of an acyl rhodium **III** is usually achieved in two ways: (i) by the insertion into aldehydes and anhydrides[1b−f] or (ii) by the insertion of CO gas into an organometallic bond.[1a] The first approach generally requires the presence of a chelating group on the aldehyde reactant to prevent competing decarbonylation. The second approach usually necessitates high pressure apparatus, heating, or often both.[3f−h,6] A drawback to these methods is that the nature of

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(2) (a) Beller, M.; Krauter, J. G. E. In *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds; Wiley-VCH: New York, 2002. Palladium: (b) Zeni, G.; Larock, R. L. *Chem. Rev.* **2006**, *106*, 4644. Cobalt: (c) Struebing, D.; Beller, M. *Top. Organomet. Chem.* **2006**, *18*, 165. (d) Klingler, R. J.; Chen, M. J.; Rathke, J. W.; Kramarz, K. W. *Organometallics* **2007**, *26*, 352.

(3) For Pauson−Khand reactions: (a) Struebing, D.; Beller, M. *Top. Organomet. Chem.* **2006**, *18*, 165. (b) Bayden, A. S.; Brummond, K. M.; Jordan, K. D. *Organometallics* **2006**, *25*, 5204. (c) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 5948. For hydroformylation reactions: (d) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665. (e) Kuil, M.; Soltner, T.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2006**, *128*, 11344. (f) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedron Lett.* **2005**, *46*, 7831. For silylformylation: (g) Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 8587. For C−H functionalization: (h) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882.

(4) (a) Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4534. (b) Cook, M. J.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 9302. (c) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514. (d) Arai, K.; Lucarini, S.; Salter, M. M.; Ohta, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 8103. (e) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591. (f) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581. (g) Cabrera, S.; Arrayas, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938.

(5) For a prime example of Rh-catalyzed desymmetrization: (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. See also: (b) McManus, H. A.; Fleming, M. J.; Lautens, M. *Angew. Chem., Int. Ed* **2007**, *46*, 433. (c) Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338. (d) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569.

(6) Evans, P. A. In *Modern Rhodium-Catalyzed Organic Reactions*; Wiley-VCH: Weinheim, Germany, 2005.

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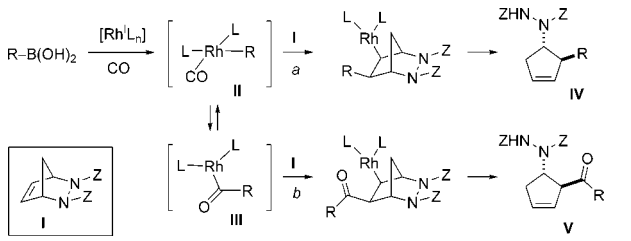
the acyl group cannot be varied easily. Consequently, a catalytic protocol which could generate easily variable acyl anion equivalents would be very useful.

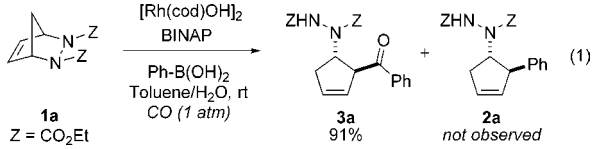
By exploiting rhodium's high affinity for CO and its reactivity with boronic acids, it is possible to generate an acyl-anion intermediate **III** (Scheme 1).[7] However, the

Scheme 1. Proposed Ring Opening with Acyl Rhodium Species



reversible process of CO insertion/extrusion favors **II** over **III** for thermodynamic reasons, and this is why high pressures are usually required.[8] Thus, in applying this catalytic system to the desymmetrization of strained alkenes **I** under ambiant conditions, it was unclear whether the desired acylrhodation (pathway b) would occur preferentially to the competing carborhodation (pathway a). Indeed, the catalytic ring-opening of diazabicycles **I** with nucleophiles toward **IV** is known with alkyls,[9] aryl groups,[10] and heteroatoms.[11] Herein, we report the chemo- and diastereoselective reaction of diazabicycles with acyl rhodium species toward **V**, which constitutes the first example of a Rh-catalyzed allylic substitution with acyl anion equivalents.

Diazabicyles **1** are attractive key substrates because of their easy preparation and stability.[12] Additionally, the ring-opened hydrazine is well recognized as an amine precursor.[13] In a test reaction, 2.0 equiv of phenylboronic acid and 1.0 equiv of bicyclic hydrazine **1a** were mixed with 10 mol % of rhodium(I) complex in the stated solvent at 23 °C, under a CO atmosphere (eq 1).

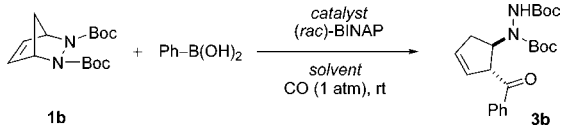


The acylated cyclopentene **3a** was obtained as the sole product in excellent yield. The absence of **2a** was surprising as it is the only product formed in the absence of CO.[14] Thus, the outcome of the reaction is completely changed by using a simple CO gas balloon instead of Ar.

Noteworthy features of the reaction are the exclusive formation of the *trans* isomer of the acylated product, the alkene in **3** does not isomerize to give the conjugated enone, and the unusual mildness of the reaction conditions for an *intermolecular* CO-insertion. The stereochemistry presumably results from addition on the alkene taking place on the *exo* face of bicycle **1**. The present ring-opening of the diaza compounds complements our previous work in the ring-opening of oxa or aza bicycles, which always gave the 1,2-*cis* ring-opened products with carbon nucleophiles.[5a,b,15]

The important optimization results are summarized in Table 1. It was found that a nonpolar, non-coordinating

Table 1. Optimization of the Ring Opening with Benzoyl Anion[a]



entry	catalyst	solvent	time (h)	yield[b] (%)
1	$[Rh(CO)_2acac]$	THF	48	38
2	$[Rh(CO)_2acac]$	dioxane	48	50
3	$[Rh(CO)_2acac]$	CH_2Cl_2	72	74
4	$[Rh(CO)_2acac]$	toluene	48	70
5	$[Rh(CO)_2acac]$	benzene/H_2O	16	92
6	$[Rh(CO)_2acac]$	toluene/H_2O	20	95
7	$[Rh(CO)_2Cl]_2$	toluene/H_2O	20	92
8	$[Rh(cod)Cl]_2$	toluene/H_2O	20	95
9	$[Rh(cod)OH]_2$	toluene/H_2O	20	91
10[c]	$[Rh(cod)OH]_2$	toluene/H_2O	20	92
11	$[Rh(cod)_2]OTf$	toluene/H_2O	20	4
12	$[Ir(cod)Cl]_2$	toluene/H_2O	20	trace
13	$Pd_2(dba)_3$	toluene/H_2O	20	0
14	$Cu(OAc)_2$	toluene/H_2O	20	0

[a] All reactions were performed using **1b** (0.135 mmol) with the listed catalyst (10 mol % in Rh), ligand (12 mol %), $PhB(OH)_2$ (2.0 equiv), and solvent (0.07 M). [b] Isolated yield. [c] Without phosphine ligand.

solvent is needed in the presence of water to obtain high yields (entries 1−6). Rhodium is the metal of choice to effect

(7) This concept was recently recognized by Castanet to generate 1,4-diketones from enones: (a) Chochois, H.; Sauthier, M.; Maerten, E.; Castanet, Y.; Mortreux, A. *Tetrahedron* **2006**, *62*, 11740. (b) Askın, O.; Dege, N.; Artok, L.; Tuerkmen, H.; Cetinkaya, B. *Chem. Commun.* **2006**, 3187. (c) Sauthier, M.; Castanet, Y.; Mortreux, A. *Chem. Commun*. **2004**, 1520.

(8) For carbonyl insertion/extrusion studies, see: (a) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674. (b) Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Chen, J.; Crabtree, R. H.; Liable-Sands, L. M.; Rheihold, A. L. *Organometallics* **1999**, *18*, 5311.

(9) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Org. Lett*. **2005**, *7*, 3605.

(10) Racemic: (a) John, J.; Sajisha, V. S.; Mohanlal, S.; Radhakrishnan, K. V. *Chem. Commun.* **2006**, 3510. Asymmetric: (b) Bertolini, F.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 9173. (c) Menard, F.; Lautens, M. Unpublished work.

(11) Luna, A. P.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett*. **2003**, *5*, 4771.

(12) Diels, O.; Bolm, J. H.; Knoll, W. *Justus Liebigs Ann. Chem.* **1925**, *443*, 242. **1b** is a free-flowing powder, making for easy handling. Its preparation on scale is convenient, involving simple filtration of the reaction mixture to obtain analytically pure material.

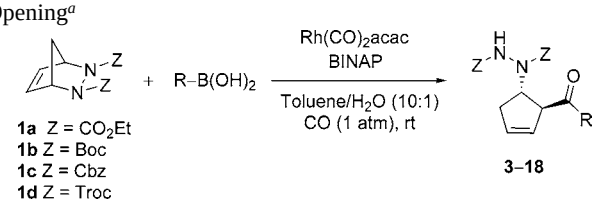
(13) (a) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614. (b) Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637. (c) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525.

(14) When the same reaction was conducted under an argon atmosphere, **2a** was obtained in >70% yield (see ref 10c). This observation suggests that when CO is present, it coordinates to Rh(I) preferentially to **1**, and that only when the acyl rhodium species is formed is the alkene **1** allowed to bind and react.

(15) Lautens, M.; Dockendorff, C. *Org. Lett*. **2003**, *5*, 3695.

the desired transformation, but the reaction is not sensitive to the rhodium source, as long as it is a neutral complex (entries 6−11). The presence of a phosphine ligand is not essential to the reaction (entries 9 and 10), yet it was found to help turnover for boronic acid partners less reactive than simple phenyl. It is proposed that the bidentate phosphine ligand creates a *reservoir* of inactive rhodium complex in solution. Thus, in view of the widespread use of BINAP ligands, it was kept as a constant parameter. As optimized conditions, [$Rh(CO)_2$acac] was chosen as a stable precatalyst with a 10:1 mixture of toluene and water as solvent mixture. The most informative results from a scope study are summarized in Table 2.

Table 2. Scope of the Acyl Rhodium(I)-Catalyzed Ring Opening[a]



entry	1	R	product	yield[b] (%)
1	**1a**	Ph	**3a**	92
2	**1b**	Ph	**3b**	91
3[e]	**1b**	Ph	**3b**	94[c]
4	**1c**	Ph	**3c**	93
5[e]	**1d**	Ph	**3d**	93
6	**1b**	4-MeO−C_6H_4-	**4**	96
7	**1b**	3-MeO−C_6H_4-	**5**	84
8	**1b**	2-Me−4-MeO−C_6H_3-	**6**	91
9	**1b**	2-Me−C_6H_4-	**7**	84
10	**1b**	3-Me−C_6H_4-	**8**	94
11	**1b**	4-Me−C_6H_4-	**9**	91
12	**1b**	2-naphthyl	**10**	88
13	**1b**	3-Me_3Si−C_6H_4-	**11**	83
14	**1b**	3-vinyl-C_6H_4-	**12**	83
15	**1b**	4-Cl−C_6H_4-	**13**	83
16	**1b**	4-F−C_6H_4-	**14**	77
17	**1b**	4-CF_3−C_6H_4-	**15**	57
18	**1b**	4-Ac−C_6H_4-	**16**	38
19	**1b**	3-thiophenyl-	**17**	39
20	**1b**	1,2-(*E*)-styryl	**18**	63[d]

[a] Unless otherwise noted, all reactions were performed using **1** (0.135 mmol) with Rh catalyst (10 mol %), (*R*)-, or *rac*-BINAP (12 mol %) in a 10:1 toluene/H_2O biphasic solvent mixture (0.07 M), under a CO gas atmosphere (balloon) for 20 h. [b] Isolated yield. [c] Reaction on 1 mmol scale. [d] Portion-wise addition of boronic acid, CsF was added (1.2 equiv). [e] Reaction time was 24 h.

The nature of the hydrazine protecting groups was found to be insignificant on the reaction outcome (entries 1−5). The reaction worked best with electron-rich and electroneutral arylboronic acids (83−96%, entries 1−14). The yield was inferior when electron-withdrawing substituents were present on the arylboronic acid moiety (38−77%, entries 16−18). The likely cause is a decreased rate of CO insertion step to form the acyl intermediate **II** for electron withdrawing groups. Alkenylboronic acids also reacted well, but slow addition of the boronic acid was required to minimize the competitive dibenzylidene acetone formation (entry 20).[16] It is remarkable that even in low-yielding reactions (**15**−**18**), none of the potentially competing arylated product **2** was observed.[17]

To date, attempts to render this reaction enantioselective did not lead to satisfactory results.[18] The rate of the phosphine-free catalyst is apparently much faster than that of a ligand-bound complex. ^{31}P NMR studies showed that phosphine ligands are displaced by CO under the reported conditions.[19] Ongoing mechanistic investigations are aimed at addressing this issue and extending the reaction to other systems.[20]

In summary, we reported the early results of a catalytic desymmetrization of strained alkenes via a formal allylic substitution reaction with acyl anion nucleophiles. The catalytic generation of acyl anion equivalents under very simple and mild conditions obviates the typical use of high pressures of CO and high reaction temperatures. The reaction allowed the rapid synthesis of *trans*-1,2-hydrazinoacyl cyclopentenes **3**, which are not easily accessible stereoselectively by other means. The densely functionalized products obtained should prove to be of great value as building blocks in organic synthesis.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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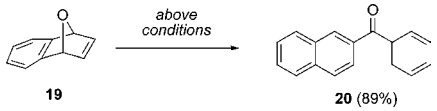
(16) Such a synthesis of symmetrical ketones was reported with organomercurials and rhodium under a CO atmosphere: Larock, R. C.; Hershberger, S. S. *J. Org. Chem.* **1980**, *45*, 3840.

(17) Even after heating, the mass balance consisted mainly of unreacted starting material.

(18) Though the arylation product **2** is formed with significant enantiomeric enrichment under the same conditions (89:11 er), the acylated product **3** was nearly racemic (55:45 er).

(19) This phenomenon was also observed by others (see ref 3f).

(20) In preliminary experiments, oxabicycle **19** reacted, but only the aromatized ketone **20** was isolated:



19 **20** (89%)