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Iridium-Catalyzed *anti*-Diastereo- and Enantioselective Carbonyl (Trimethylsilyl)allylation from the Alcohol or Aldehyde Oxidation Level

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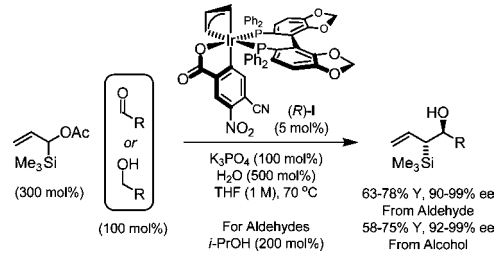
Abstract: Using the *ortho*-cyclometalated π-allyl iridium precatalyst (*R*)-**I** derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, (*R*)-SEGPHOS, and allyl acetate, enantioselective transfer hydrogenation of α-(trimethylsilyl)allyl acetate in the presence of aldehydes **2a**−**i** mediated by 2-propanol delivers products of (trimethylsilyl)allylation **4a**−**i** in good isolated yields and with exceptional levels of *anti*-diastereoselectivity and enantioselectivity (90−99% ee). In the absence of 2-propanol, but under otherwise identical reaction conditions, carbonyl (trimethylsilyl)allylation is achieved directly from the alcohol oxidation level to furnish an equivalent set of adducts **4a**−**i** with roughly equivalent isolated yields and stereoselectivities. To evaluate the synthetic utility of the reaction products **4a**−**i**, adduct **4g** was converted to the 1,4-ene-diol **5g** via dioxirane-mediated oxidative desilylation with allylic transposition, the allylic alcohol **6g** via protodesilylation with allylic transposition, and the γ-lactam **7g** via chlorosulfonyl isocyanate-mediated cycloaddition.

Introduction

In connection with studies aimed at the discovery of hydrogen-mediated reductive C−C bond formations beyond hydroformylation, we recently uncovered a broad family of C−C bond forming transfer hydrogenations promoted by iridium and ruthenium catalysts.[1] A remarkable feature of these processes resides in the ability to achieve carbonyl addition from the aldehyde or alcohol oxidation level. In the former case, 2-propanol or formic acid mediates reductive C−C coupling. In the latter case, dehydrogenation of the primary alcohol reactants generates aldehyde electrophiles, while simultaneously driving reductive generation of organometallic nucleophiles from *p*-unsaturated reactants. Using *ortho*-cyclometalated iridium catalysts, highly enantioselective protocols for carbonyl allylation,[2a,b,e−h,j] crotylation,[2c,f,j] and *tert*-prenylation[2d,f,j] from the alcohol or aldehyde oxidation level were devised. More recently, related catalytic enantioselective methods carbonyl (hydroxy)allylation and (hydroxymethyl)allylation were developed.[3] Unlike conventional methods for carbonyl allylation,[4] these processes circumvent the use of premetalated nucleophiles and metallic reductants.[1−3]

Scheme 1. Iridium-Catalyzed Anti-Diastereo- and Enantioselective Carbonyl (trimethylsilyl)allylation from the Alcohol or Aldehyde Oxidation Level



Here, using the isolated *ortho*-cyclometalated π-allyl iridium precatalyst derived from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, (*R*)-SEGPHOS,[5] and allyl acetate, we report that α-(trimethylsilyl)allyl acetate[6] **1a** couples to carbonyl compounds from the aldehyde or alcohol oxidation level, respectively, with exceptional levels of regio- and *anti*-diastereo- and enantiose-

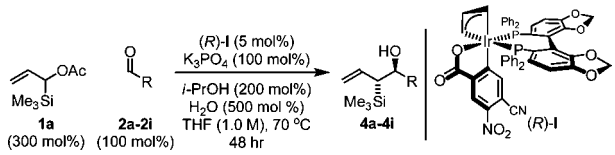
(1) For selected reviews, see: (a) Ngai, M.-Y.; Kong, J. R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (c) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (d) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichim. Acta* **2008**, *41*, 95. (e) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34.

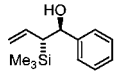
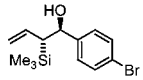
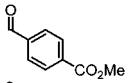
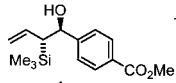
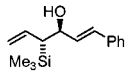
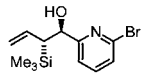
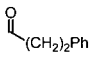
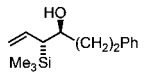
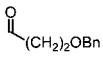
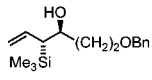
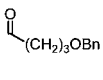
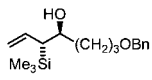
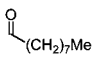
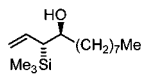
(2) For enantioselective carbonyl allylation, crotylation, and reverse prenylation via iridium-catalyzed C-C bond-forming transfer hydrogenation, see: (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Kim, I. S.; Han, S. B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (d) Han, S. B.; Kim, I. S.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6916. (e) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018. (f) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6316. (g) Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3108. (h) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112. (i) For a recent application in total synthesis, see Harsh, P.; O'Doherty, G. A. *Tetrahedron* **2009**, *65*, 5051. (j) Bechem, B.; Patman, R. L.; Hashmi, S.; Krische, M. J. *J. Org. Chem.* **2010**, *75*, 1795.

(3) For enantioselective carbonyl (hydroxy)allylation and (hydroxymethyl)allylation via iridium-catalyzed C-C bond-forming transfer hydrogenation, see: (a) Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760. (b) Zhang, Y. J.; Yang, J. H.; Kim, S. H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 4562.

(4) For selected reviews on enantioselective carbonyl allylation and crotylation, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23. (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (f) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (g) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (h) Hall, D. G. *Synlett* **2007**, 1644.

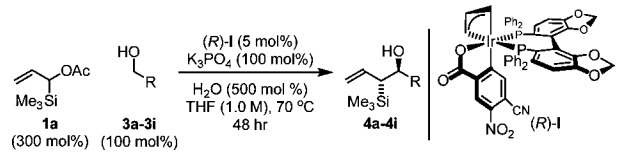
Table 1. Enantioselective α-(Trimethylsilyl)allylation from the Aldehyde Oxidation Level[a]

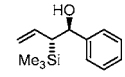
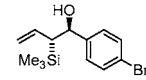
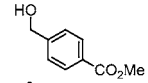
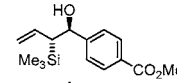
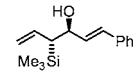
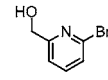
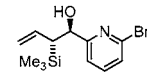
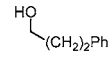
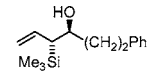
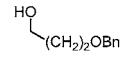
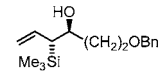
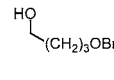
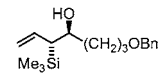
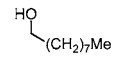
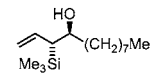


Entry	Aldehyde	Product	Yield, dr, ee%
1	 2a	 4a	71% Yield ≥ 99:1 dr 96% ee
2	 2b	 4b	73% Yield ≥ 99:1 dr 98% ee
3	 2c	 4c	78% Yield ≥ 99:1 dr 98% ee
4	 2d	 4d	74% Yield ≥ 99:1 dr 94% ee
5	 2e	 4e	66% Yield ≥ 99:1 dr 99% ee
6	 2f	 4f	69% Yield ≥ 99:1 dr 98% ee
7	 2g	 4g	63% Yield 4:1 dr 98% ee
8	 2h	 4h	69% Yield ≥ 99:1 dr 98% ee
9	 2i	 4i	72% Yield ≥ 99:1 dr 90% ee

[a] Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details.

Table 2. Enantioselective α-(Trimethylsilyl)allylation from the Alcohol Oxidation Level[a]



Entry	Aldehyde	Product	Yield, dr, ee%
1	 3a	 4a	69% Yield ≥ 99:1 dr 96% ee
2	 3b	 4b	72% Yield ≥ 99:1 dr 96% ee
3	 3c	 4c	75% Yield ≥ 99:1 dr 98% ee
4	 3d	 4d	70% Yield ≥ 99:1 dr 92% ee[b]
5	 3e	 4e	58% Yield ≥ 99:1 dr 99% ee
6	 3f	 4f	65% Yield ≥ 99:1 dr 97% ee
7	 3g	 4g	61% Yield 98:2 dr 90% ee
8	 3h	 4h	69% Yield ≥ 99:1 dr 95% ee
9	 3i	 4i	67% Yield ≥ 99:1 dr 95% ee

[a] As described for Table 1. [b] The complex modified by (*R*)-C3-TUNEPHOS was used as precatalyst.

lectivity (Scheme 1). In this fashion, α-(trimethylsilyl)allyl acetate serves as an alternative to previously reported silicon-containing 1,3- or 1,1-bimetallic allyl transfer agents.[7−11] As demonstrated in the case of adduct **4g**, the products of (trimethylsilyl)allylation are readily converted to 1,4-ene-diols upon DMDO oxidation.[8h,i] Additionally, conditions for proto-desilylation with allylic transposition have been identified in the absence of a hydroxyl protecting group. Finally, upon exposure to chlorosulfonyl isocyanate, formal [3 + 2] cycloaddition occurs to deliver γ-lactams possessing three contiguous stereogenic centers as single diastereomers.

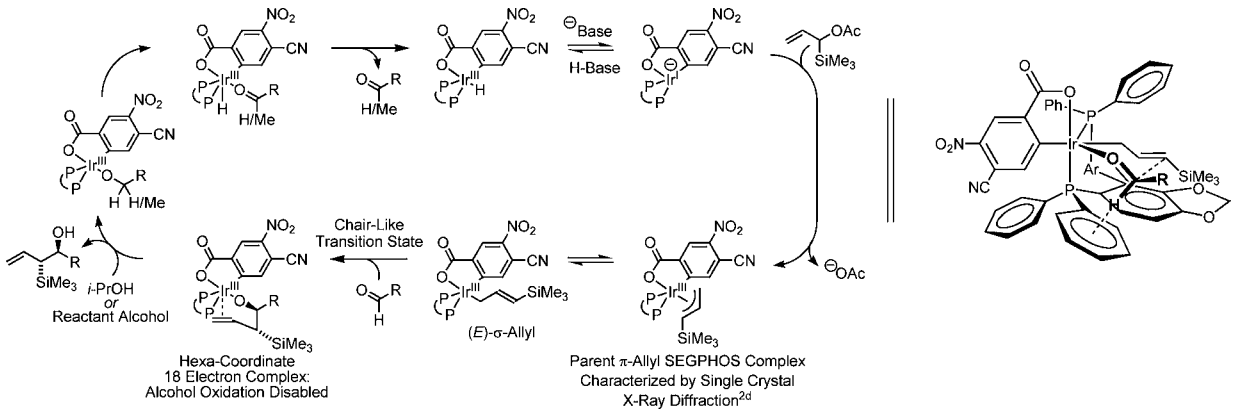
Results and Discussion

Our study began with the attempted (trimethylsilyl)allylation of benzyl alcohol **3a**. Using the *ortho*-cyclometalated catalyst generated in situ from $[Ir(cod)Cl]_2$, 4-cyano-3-nitrobenzoic acid, (*R*)-SEGPHOS,[5] and allyl acetate, neither the desired (trimethylsilyl)allylation product **4a** nor the resulting Peterson olefination product was detected. Using the isolated π-allyl iridium precatalyst (*R*)-**I** in the presence of cesium carbonate, the desired

(5) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal* **2001**, *343*, 264. For single crystal x-ray diffraction analysis of a closely related *ortho*-cyclometalated iridium π-allyl complex modified by (*S*)-SEGPHOS, see ref 2d.

(6) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.-M.; Szczepanski, S. W. *Org. Synth.* **1988**, *66*, 14. A modification of this literature protocol was used to prepare α-(trimethylsilyl)allyl acetate. See Supporting Information for experimental details.

Scheme 2. Proposed Catalytic Mechanism and Stereochemical Model for Carbonyl (Trimethylsilyl)allylation from the Alcohol or Aldehyde Oxidation Level



(trimethylsilyl)allylation product **4a** was formed along with substantial quantities of Peterson olefination product. After various inorganic bases were screened, it was found that Peterson olefination is suppressed using K_3PO_4 (1.0 equiv) in the presence of water (5.0 equiv) for reactions conducted at 70 °C. Under these conditions, α-(trimethylsilyl)allyl acetate **1a** was coupled to a structurally diverse set of aldehydes **2a**−**i** (Table 1). In each case, good isolated yields were accompanied by exceptional levels of diastereo- and enantioselectivity. In the absence of 2-propanol, but under otherwise identical conditions, (trimethylsilyl)allylation occurs directly from the alcohol oxidation level to furnish an identical set of adducts **4a**−**i** (Table 2). Again, good isolated yields were accompanied by exceptional levels of diastereo- and enantioselectivity. Thus, unlike corresponding protocols involving allylmetal reagents,[7−11] carbonyl (trimethylsilyl)allylation occured with equal facility from the alcohol or aldehyde oxidation level.

The mechanism for catalytic carbonyl (trimethylsilyl)allylation is analogous to that previously proposed for related crotylations.[2c] However, complete levels of *anti*-diastereoselectivity are observed in nearly all cases, suggesting that carbonyl addition occurs exclusively from the (*E*)-σ-allyl through a chairlike transition structure. Notably, although the catalyst dehydrogenates primary alcohols **3a**−**i**, the reaction products **4a**−**i**, which are homoallylic alcohols, are not oxidized under the coupling conditions and, hence, do not experience any erosion of enantiomeric purity by way of redox equilibration. This result is remarkable, as 2-propanol, a secondary alcohol, is oxidized under the coupling conditions when aldehydes **2a**−**i** are employed as reactants. As indicated in the proposed catalytic mechanism (Scheme 2), coordination of iridium to the homoallylic olefin of reaction products **4a**−**i** provides a hexacoordinate, 18-electron complex that cannot engage in β-hydride elimination due to the absence of an open coordination site.

To evaluate the utility of the coupling products **4a**−**i**, adducts **4a**, **4f**, **4g**, and **4i** were subjected to DMDO-mediated oxidative elimination.[8h,i] The 1,4-ene-diols **5a**, **5f**, **5g**, and **5i** were produced in excellent yield with high levels of (*E*:*Z*)-selectivity (Scheme 3). Proto-desilylation was attempted next. Under nearly all conditions assayed, exclusive formation of Peterson olefination products was observed. However, upon exposure of adduct **4g** to $TiCl_4$ in the presence of exogenous aldehyde, the product of proto-desilylation **6g** was generated in 73% yield with complete (*E*:*Z*)-selectivity (Scheme 4). In the absence of aldehyde, Peterson olefination was again the exclusive reaction product, suggesting that exogenous aldehyde protects the hydroxyl moiety of **4g** through formation of a titanium-bound hemiacetal. Notably, compound **6g** was previously prepared in seven steps from malic acid.[12] Thus far, the proto-desilylation is most efficient for the benzyl ether-containing adduct **4g** (Scheme 4).

(7) For examples of carbonyl additions employing 1,3-bimetallic allyl transfer agents where $M_1 = M_2 = Si$, see: (a) Corriu, R.; Escudie, N.; Guerin, C. *J. Organomet. Chem.* **1984**, *264*, 207. (b) Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646. (c) Restorp, P.; Dressel, M.; Somfai, P. *Synthesis* **2007**, 1576. (d) Tuzina, P.; Somfai, P. *Tetrahedron Lett.* **2008**, *49*, 6882.

(8) For examples of carbonyl additions employing 1,3-bimetallic allyl transfer agents where M_1 = B, M_2 = Si, see: (a) Yatagai, H.; Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 4548. (b) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751. (c) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229. (d) Tsai, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236. (e) Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387. (f) Roush, W. R.; Grover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563. (g) Roush, W. R.; Grover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567. (h) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243. (i) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981. (j) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 501. (k) Marron, T. G.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 1581. (l) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112. (m) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461. (n) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413. (o) Shimizu, M.; Kitagawa, H.; Kurahashi, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 4283. (p) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (q) Tinsely, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818. (r) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960. (s) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315. (t) Huh, C. W.; Roush, W. R. *Org. Lett.* **2008**, *10*, 3371.

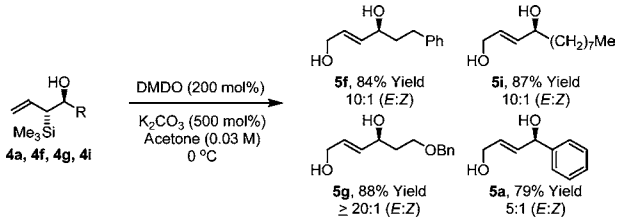
(9) For examples of carbonyl additions employing 1,3-bimetallic allyl transfer agents where $M_1 = Si$, $M_2 = Ti$, see: (a) Sato, F.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **1982**, *23*, 4589. (b) Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259. (c) Reetz, M. T.; Steinbach, R.; Westerman, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441. (d) Ikeda, Y.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 657. (e) Ducray, R.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4688. (f) de Fays, L.; Adam, J.-M.; Ghosez, L. *Tetrahedron Lett.* **2003**, *44*, 7197.

(10) For examples of carbonyl additions employing 1,3-bimetallic allyl transfer agents where $M_1 = Si$, $M_2 = Cr$, see: (a) Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1992**, *33*, 4761. (b) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.

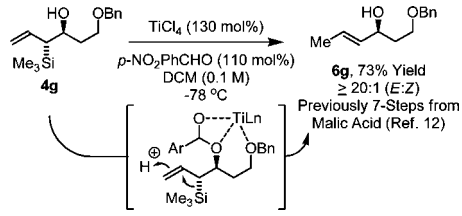
(11) For examples of carbonyl additions employing 1,3-bimetallic allyl transfer agents where $M_1 = Si$, $M_2 = Sn$, see: (a) Lautens, M.; Ben, R. N.; Delanghe, P. H. M. *Tetrahedron* **1996**, *52*, 7221.

(12) Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011, and references cited therein.

Scheme 3. Dioxirane-Mediated Oxidative Desilylation of Adducts **4a**, **4f**, **4g**, and **4i** to Furnish the Corresponding 1,4-Ene-diols **5a**, **5f**, **5g**, and **5i**



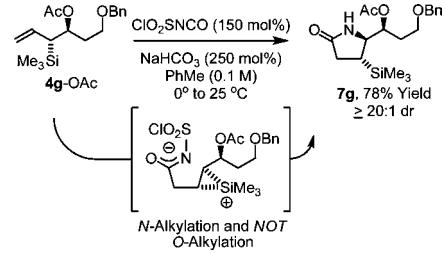
Scheme 4. Protodesilylation of **4g** Requires Exogenous Aldehyde to Suppress Peterson Olefination



Finally, under conditions similar to those described by Woerpel,[13] exposure of **4g**-OAc to chlorosulfonyl isocyanate delivers the product of [3 + 2] cycloaddition, the 4,5-trans-disubstituted pyrrolidinone **7g**, as a single diastereomer. Lactone formation is not observed. Formation of the **7g** suggests a mechanism involving stereoselective addition of chlorosulfonyl isocyanate to the allylsilane antiperiplanar with respect to the silyl group to generate the indicated β-silyl carbocation. Exclusive *N*-cyclization accompanied by 1,2-silyl migration delivers the 4,5-trans-substituted pyrrolidinone **7g**. In the absence of $NaHCO_3$, a mixture of lactone and lactam products are observed. These data suggest that partitioning of the *N*- and *O*-cyclization pathways is not dictated primarily by steric factors as proposed by Woerpel,[13b] but that the acidity of the medium plays a dominant role (Scheme 5).

(13) (a) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434, and references cited therein. (b) Peng, Z.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675.

Scheme 5. Reaction of Adduct **4g** with Chlorosulfonyl Isocyanate to Furnish the Product of Formal [3 + 2] Cycloaddition **7g**



Conclusion

In summary, we report a highly *anti*-diastereo- and enantioselective carbonyl (trimethylsilyl)allylation under the conditions of iridium catalyzed transfer hydrogenation employing a single-component catalyst, the *ortho*-cyclometalated complex (*R*)-**I**. Notably, identical sets of adducts **4a**−**i** were formed with comparable levels of selectivity from the aldehyde or alcohol oxidation level in the absence of Peterson olefination. Oxidative desilylation of adducts **4a**, **4f**, **4g**, and **4i** employing DMDO provided access to highly enantiomerically enriched 1,4-ene-diols **5a**, **5f**, **5g**, and **5i**.[8h,i] Conditions for proto-desilylation with allylic transposition were identified for adduct **4g** in the absence of a hydroxyl protecting group. Finally, exposure of adduct **4g** to chlorosulfonyl isocyanate delivered 4,5-trans-disubstituted pyrrolidinone **7g** as a single diastereomer. Future studies will focus on the development of related unsaturated alcohol C−C couplings and related imine additions from the amine oxidation level.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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