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Gold-Catalyzed and *N*-Iodosuccinimide-Mediated Cyclization of γ-Substituted Allenamides

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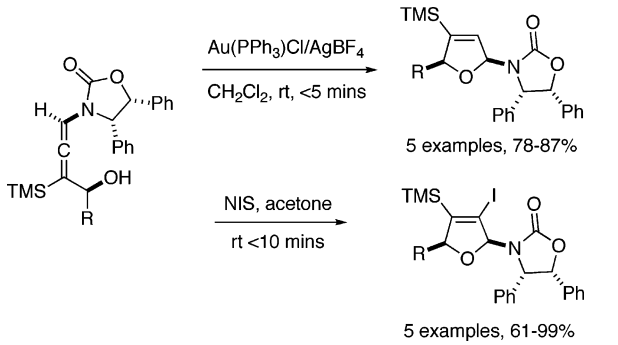
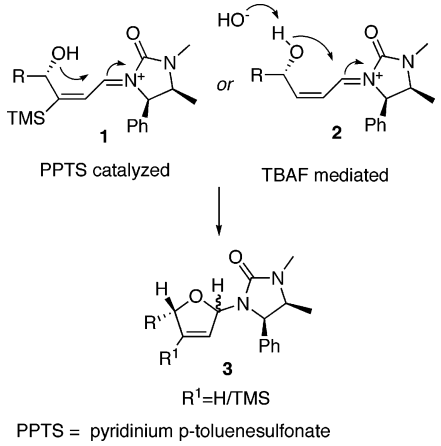


Chiral γ-substituted allenamides have been shown to undergo efficient gold-catalyzed and *N*-iodosuccinimide-mediated cyclization to highly functionalized dihydrofurans. These reactions proceed rapidly and without loss of stereochemistry.

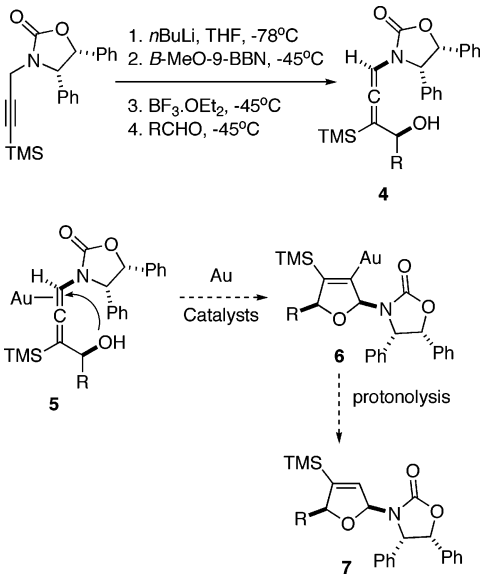
Chiral allenamides have recently proven to be important synthetic intermediates, undergoing a variety of interesting transformations.[1] Recently, Hsung et al. reported the Brønsted acid-catalyzed and TBAF-mediated cyclization of γ-substituted allenamides to give 2,5-disubstituted dihydrofurans **3**.[2] These cyclizations displayed no or poor diastereoselectivity, which was likely due to the possibility of *re* or *si* face attack on proposed vinyliminium intermediates **1** and **2** (Scheme 1).

Interestingly, the authors observed that the analogous oxazolidinones were unreactive to their conditions and proposed that this was due to the electronegativity difference between nitrogen and oxygen. We have recently developed a boron-mediated stereoselective synthesis of chiral γ-substituted allenamides **4** bearing an oxazolidinone (Scheme 2).[3] We reasoned that these substrates might be activated toward nucleophilic cyclization by transition-metal catalysis.[4] Notably, Krause et al. have shown that chiral α-hydroxyallenes undergo gold-catalyzed cycloisomerization to 2,5-dihydrofurans without loss of stereochemistry.[5] If allenamide **4** is activated in a similar manner (**5**), then cyclization should proceed without loss of stereochemistry to yield stereodefined dihydrofuran **7**.

SCHEME 1



SCHEME 2



To test this hypothesis, allenamide **4a** (R = Ph) was treated with 5 mol % $Au(PPh_3)Cl/AgBF_4$ in CH_2Cl_2 at rt (Scheme 3).[6] The reaction proceeded to completion in under 5 min to yield 2,5-dihydrofuran **7a** as a single diastereoisomer. Interestingly, if the reaction was left for an extended period of time (>30 min), a second compound, the *trans* diastereoisomer **8**, was formed.[7] We assume that this *trans* diastereoisomer is formed from the *cis* diastereoisomer via gold-catalyzed ring-opening to iminium **9**; reclosure via *si* or *re* face attack can then occur to either the *cis*- or *trans*-dihydrofuran, respectively (Scheme 3). Kobayashi et al. have proposed a similar intermediate iminium ion in their Lewis acid-catalyzed ring-opening reactions of *N*,*O*-acetals and successfully trapped it with a variety of nucleophiles.[8] However, attempts to trap iminium ion **9** with

(1) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773.
(2) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challeppan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038.
(3) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2005**, *70*, 8628.
(4) For a review on nucleophilic transition-metal-based cyclization of allenes, see: Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12.
(5) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537.
(6) Only traces of product were observed with $Au(PPh_3)Cl$ in the absence of $AgBF_4$.
(7) The structure of this compound was determined by X-ray crystallography (see the Supporting Information).
(8) Sugiura, M. Kobayashi, S. *Org. Lett.* **2001**, *3*, 477

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SCHEME 3

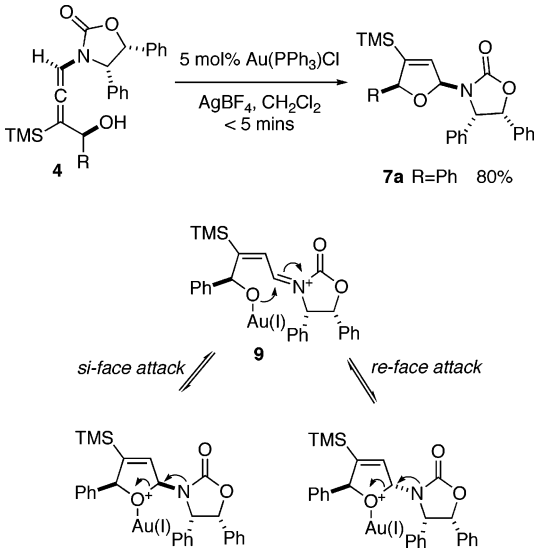


TABLE 1. Gold-Catalyzed Cyclizations of Allenes 4 (Scheme 3)[a]

Allene	R	Product	Yield, %[b]
4a	Ph	**7a**	80%
4b	*i*Pr	**7b**	87%
4c		**7c**	86%
4d		**7d**	78%
4e		**7e**	81%

[a] All reactions were conducted in CH_2Cl_2 (0.1 M) at rt with 5 mol % $Au(PPh_3)Cl/AgBF_4$. Aside from **4d** all allenes used were racemic. [b] Reported yields are for isolated, purified compounds.

allyltrimethylsilane or (TMS)CN resulted only in recovery of a mixture of *cis*- and *trans*-dihydrofurans.

An NMR experiment was conducted to monitor the course of the reaction, and it was found that after 1 h the reaction had equilibrated to a 2.7:1 *trans*/*cis* mixture of dihydrofurans.[9] Also, if the isolated *cis*-dihydrofuran was subsequently subjected to Au(I) catalysis for an extended period of time, formation of the *trans* diastereoisomer was also observed. If the $AuCl_3$ was used in place of the Au(I) catalyst, then the same cyclization was observed, but the formation of the *trans* diastereosiomer was more rapid, and the reaction was accompanied by significant decomposition;[10] this was presumably due to the more Lewis-acidic nature of the Au(III) catalyst.

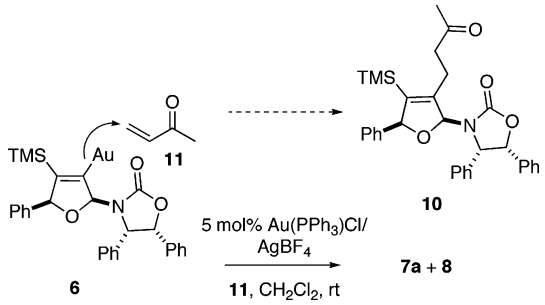
A range of allenes were subjected to the same cyclization conditions (Table 1), and all proceeded in excellent yields to give the corresponding dihydrofurans as single *cis* diastereoisomers.

The products are versatile synthetic intermediates, and dihydrofuran **7e** is of particular note as it is a potential

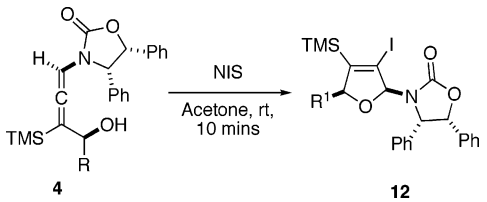
(9) Reaction of **4** (10 mg, 0.022 mmol, 1 equiv) was carried out in 0.5 mL of $CDCl_3$ with 5 mol % $Au(PPh_3)Cl$ and $AgBF_4$.

(10) Peaks in the crude NMR indicated that decomposition to the furan may be taking place.

SCHEME 4



SCHEME 5



nucleoside analogue. In addition, they all feature a vinylsilane moiety, which should allow funtionalization at C-4.[11] However, we were also interested in opening up functionalization at C-3 and envisioned that this might be possible via in situ trapping of the gold intermediate **6** with α,β-unsaturated enones to yield **10** (Scheme 4). Similar electrophilic trapping of gold−arene intermediates has been observed in furan and indole systems.[12] Unfortunately, when the cyclization was carried out in the presence of methyl vinyl ketone (**11**), only protodesilyation was observed with $Au(PPh_3)Cl/AgBF_4$ or $AuCl_3$.

To provide a handle for elaboration at C-3, attention was turned to alternative electrophilic activation methods for cyclizations of allenamides **4**. *N*-Bromosuccinimide (NBS) has been shown to activate allenylcarbinols toward cyclization, resulting in the formation of bromodihydrofurans.[13] A similar cyclization on allenamides **4** would yield a vinyl halide at C-3 and thus open up the possibility of coupling chemistry to functionalize this position. We opted to employ *N*-iodosuccinimide (NIS) rather than NBS as this would result in a more reactive vinyl iodide as the product. Pleasingly, upon treatment with NIS in acetone a rapid cyclization was observed (<10 min) without any loss of stereochemistry, yielding *cis*-iododihydrofurans **12** (Scheme 5, Table 2).

The vinyl iodide functionality present in dihydrofurans **12** should allow a range of functionalization by metal-catalyzed coupling chemistry.[14] To demonstrate this, a Suzuki coupling with phenylboronic acid and **12a** was carried out (Scheme 6). Under standard thermal conditions, the reaction proved to be sluggish, with only 50% conversion to **14** being observed after 24 h at reflux in toluene. This is likely due to the hindered and electron-rich nature of the vinyl iodide, which would result in a slow oxidative insertion step. However, under microwave irradiation a much more rapid reaction was observed (30 min total reaction time) that went to 100% conversion if the catalyst was added in two 5 mol % portions.

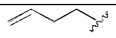
(11) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(12) (a) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265. (b) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-K.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285

(13) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 2995.

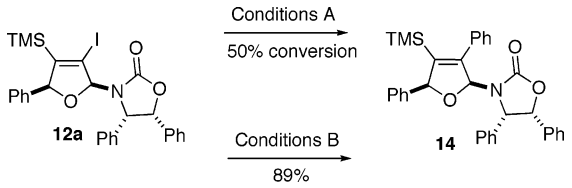
(14) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

TABLE 2. NIS-Mediated Cyclizations of Allenes (Scheme 5)[a]

Allene	R	Product	Yield, %[b]
4a	Ph	**12a**	99%
4b	*i*Pr	**12b**	99%
4c		**12c**	94%
4d		**12d**	70%
4e		**12e**	61%

[a] All reactions were conducted with NIS (1.2 equiv) in acetone (0.1 M) at rt. Aside from **4d**, all allenes used were racemic. [b] All yields are for isolated and purified compounds.

SCHEME 6[a]



[a] Conditions: (A) $Pd(PPh_3)_4$ (10 mol %), $PhB(OH)_2$, Na_2CO_3, PhMe, reflux for 24 h; (B) $Pd(PPh_3)_4$ (10 mol %), $PhB(OH)_2$, Na_2CO_3, DMF, microwave irradiation of 120 W, 180 °C, 275 psi, 3 × 10 min.

In conclusion, we have developed efficient gold-catalyzed and NIS-mediated cyclizations of allenamides **4** for the synthesis of highly functionalized dihydrofurans. In particular, dihydrofurans **7e** and **12e** should be useful scaffolds for the synthesis of nucleoside analogues by coupling and/or vinylsilane chemistry.

Experimental Section

General Procedure for the Gold-Catalyzed Cyclizations of Allenylcarbinols. To a solution of the allenylcarbinol **4** in CH_2Cl_2 (0.1 M) were added $Au(PPh_3)Cl$ (0.05 equiv) and $AgBF_4$ (0.05 equiv). After TLC analysis showed the reaction to be complete it was diluted with CH_2Cl_2 and filtered through a plug of neutral alumina. Evaporation to dryness and purification by flash chromatography (30% EtOAc/hexanes) gave dihydrofuran **7** as a single diastereoisomer.

(4*R*,5*S*)-4,5-Diphenyl-3-((2*S*,5*S*)-5-phenyl-4-(trimethylsilyl)-2,5-dihydrofuran-2-yl)oxazolidin-2-one. This compound was made according to the general procedure, using allenylcarbinol **4a** to give dihydrofuran **7a** as a pale yellow solid (12 mg, 81%). Mp: 139−141 °C. ^{1}H NMR[15] (300 MHz, $CDCl_3$): δ 7.22−7.27 (m, 3H), 7.09−7.14 (m, 8H), 6.91−6.99 (m, 4H), 6.42 (dd, J = 2.4, 1.5 Hz, 1H), 5.93 (dd, J = 3.9, 1.2 Hz, 1H), 5.85 (d, J = 8.1 Hz, 1H), 5.59 (dd, J = 3.9, 2.4 Hz, 1H), 5.23 (d, J = 8.1 Hz, 1H), −0.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 148.6, 140.4, 134.9, 134.7, 134.3, 128.8, 128.6, 128.6, 128.4, 128.2, 128.1, 128.1, 127.3, 126.4, 92.3, 91.2, 80.4, 64.6, −1.4. IR: 1762 cm^{-1}. HRMS (FAB$^+$) (M + H): *m*/*z* calcd for $C_{28}H_{29}NO_3Si$, 456.1912; found, 456.1906. Anal. Calcd for $C_{28}H_{29}NO_3Si$: C, 73.81; H, 6.42; N, 3.07. Found: C, 73.44; H, 6.41; N, 3.05.

(4*R*,5*S*)-4,5-Diphenyl-3-((2*R*,5*S*)-5-phenyl-4-(trimethylsilyl)-2,5-dihydrofuran-2-yl)oxazolidin-2-one (8). Mp: 181−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28−7.34 (m, 3H), 7.18−7.28 (m, 2H), 7.08−7.10 (m, 5H), 6.96−7.07 (m, 5H), 6.94−6.94 (m, 1H), 5.90 (d, J = 8.7 Hz, 1H), 5.85 (dd, J = 8.7, 2.1 Hz, 1H), 5.42−5.43 (m, 1H), 5.15 (d, J = 8.7 Hz, 1H), −0.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 148.6, 140.4, 137.0, 134.8, 134.0, 128.8, 128.7, 128.6, 128.2, 128.0, 127.9, 127.3, 126.3, 93.2, 91.9 80.5, 61.3, −2.1. IR: 1762 cm^{-1}. HRMS (FAB$^+$) (M + H): *m*/*z* calcd for $C_{28}H_{29}NO_3Si$, 456.1912; found, 456.1929. Anal. Calcd for $C_{28}H_{29}NO_3Si$: C, 73.81; H, 6.42; N, 3.07. Found: C, 73.65; H, 6.52; N, 3.03.

General Procedure for the NIS-Catalyzed Cyclizations of Allenylcarbinols. To a solution of the allenylcarbinol **4** (1 equiv) in CH_2Cl_2 (0.1 M) was added *N*-iodosuccinimide (1.2 equiv), and the reaction was carefully monitored by TLC until all the starting material was consumed (typically <10 min). The reaction mixture was then filtered through a short plug of neutral alumina and purified by flash column chromatography (typically 20% EtOAc/hexanes).

(4*S*,5*R*)-3-((2*S*,5*S*)-3-Iodo-5-phenyl-4-(trimethylsilyl)-2,5-dihydrofuran-2-yl)-4,5-diphenyloxazolidin-2-one. This compound was made according to the general procedure, using allene **4a** to give the iododihydrofuran **12a** as a white solid (25.5 mg, 99%). Mp: 110−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02−7.15 (m, 6H), 6.85−6.94 (m, 9H), 6.08 (d, J = 4.0 Hz, 1H), 5.84 (d, J = 8.0 Hz, 1H), 5.47 (d, J = 4.0 Hz, 1H), 5.18 (d, J = 8.0 Hz, 1H), −0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 151.7, 138.8, 134.4, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 126.7, 100.9, 95.4, 93.4, 81.1, 63.2, −1.2. IR: 1767 cm^{-1}. HRMS (FAB$^+$) (M + H): *m*/*z* calcd for $C_{29}H_{41}NO_4Si_2I$, 650.1619; found, 650.1645. Anal. Calcd for $C_{29}H_{41}NO_4Si_2I$: C, 57.83; H, 4.85; N, 2.41. Found: C, 58.00; H, 5.02; N, 2.40.

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Supporting Information Available: X-ray structural data for **8** (CIF), characterization data for **7b**−**e** and **12b**−**e**, and ^{1}H and ^{13}C spectra for **12c**, **12e**, **14**, **7b**, **7c**, and **7e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Tentative assignment for ^{1}H NMR: δ 7.22−7.27 (m, 3H, Ar), 7.09−7.14 (m, 8H, Ar), 6.91−6.99 (m, 4H, Ar), 6.42 (m, 1H, C-2), 5.93 (dd, J = 3.9, 1.2 Hz, 1H, C-3), 5.85 (d, J = 8.1 Hz, 1H, C-5 oxazolidinone), 5.59 (m, 1H, C-5), 5.23 (d, J = 8.1 Hz, 1H, C-4 oxazolidinone), −0.10 (s, 9H, TMS).