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Stereodivergent Metal-Catalyzed Allene Cycloisomerizations

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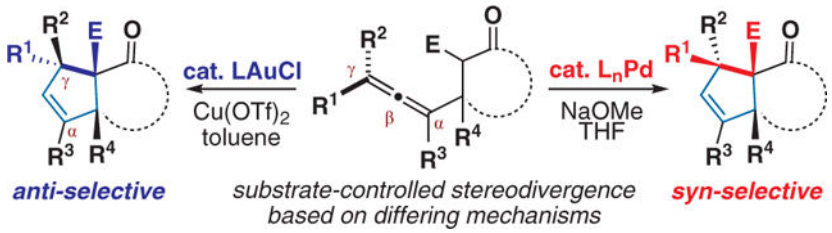
Abstract

Metal-catalyzed allene cycloisomerizations provide rapid entry into five-membered carbocyclic frameworks, a common motif in natural products and pharmaceuticals. While both Au(I) and Pd(0)-catalyzed allene cycloisomerizations give 5-*endo*-*dig* cyclization, Pd prefers the *syn* diastereomer in contrast to the *anti* isomer observed with Au. The change in stereoselectivity is proposed to arise from buildup of $A^{1,3}$ strain during the key carbopalladation step to furnish the cycloisomerized products in moderate to good *dr* with yields comparable to Au(I) catalysts.

Graphical Abstract



Keywords

allene; cycloisomerization; cyclopentene; Conia-ene; carbopalladation; carbocycle

Methods capable of rapidly transforming simple precursors into stereochemically rich and densely functionalized five-membered carbocycles continue to be of interest the synthetic community, due to the ubiquity of cyclopentanes in pharmaceuticals, natural products, and other molecules of biological interest.[1] Chiral allenes, 1,2-dienes with a unique element of axial chirality, have been underutilized in synthetic methods development, due to the misconception they are hard to prepare and unstable. Indeed, our group and many others have demonstrated the versatility and power of these manifolds for the preparation of highly substituted carbo- and heterocycles with high levels of chemo-, regio- and stereoselectivity.[2]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610746.

Metal-catalyzed, Conia-ene-like intramolecular additions of carbon nucleophiles to allenes using Pd[3] and Au[4] catalysts are known; however, the majority of reported examples employ achiral allenes and homochiral nucleophiles, which limits the diversity of products that might be formed from a single precursor. A more versatile strategy is shown in Scheme 1 (A), where treatment of a chiral allene with an appropriate metal catalyst forms a π-allyl complex that can be attacked at either the α or γ carbon; depending on the stereochemistry of the resulting alkene, four possible products can be generated. Use of a prochiral carbon nucleophile further complicates the picture, as the presence of stereoisomers results in the potential for 16 different products.

In our previous studies of Au-catalyzed allene cycloisomerization[5] (Scheme 1, B), the selectivity issue was partially addressed by tethering the nucleophile to the allene, such that 5-*endo* attack at the γ carbon is preferred. The *anti* relationship between R^1 at C5 and E at C1, as well as the *syn* orientation of E and H at the C1/C2 ring juncture, were proposed to arise from minimization of $A^{1,3}$-strain and steric congestion in the key Au(I) η^1-allyl cationic intermediate.[5] We hypothesized a catalyst that forms products through a different mechanistic pathway might provide a stereodivergent synthesis of these highly substituted bicy clic cyclopentenes. In this paper, we report a Pd-catalyzed allene cycloisomerization that favors a *syn* relationship between C1 and C5 (Scheme 1, B).

In order to identify conditions suitable for stereodivergent cycloisomerization, several reported conditions were evaluated utilizing allene **1a** (Table 1). The use of either Lewis[6] or Brønstead[7] acids (Table 1, entries 1 and 2) did not furnish the desired **2a**; similarly, despite reports that the acidic C–H bond of the malonate is sufficient to promote effective reactivity,[8] no **2a** was detected in the absence of additive (Table 1, entry 3). Addition of $Cu(OTf)_2$ (Table 1, entry4) furnished 15% of the desired **2a**; however, the major product resulted from isomerization to the corresponding 1,3-diene.

The lack of reactivity under acidic conditions was surmised to result from ineffective formation of the nucleophile; thus, attention turned to basic additives capable of generating the nucleophile *in situ*. Nitrogen bases gave only trace **2a** (Table 1, entries 5–7); while NaH (Table 1, entry 8) gave complete deprotonation of the malonate, only trace **2a** was observed. This suggested that not only must the base be strong enough to completely deprotonate the malonate, but its conjugate acid must also be capable of promoting protodemetallation of a proposed vinyl-Pd species (Scheme 2, *vide infra*) to liberate the product and turn over the catalytic cycle. Carbonate bases (Table 1, entries 9–11) gave variable success, depending on solubility, with Cs_2CO_3 providing **2a** in 53% yield. Further improvements were observed with NaOMe (Table 1, entries 12 and 13), likely due to the ability of the released MeOH to protonate the vinyl Pd intermediate. Other solvents, additives, and conditions gave incomplete conversion or isomerization into the corresponding 1,3-diene (see the Supporting Information for additional details).

Efforts to optimize the *dr* in favor of the *syn*-**2a** focused on modifications to the ligand on Pd (Table 2). Neocuproine[9] (Table 2, entry 1) formed **2a** in 71% yield with a slight preference for the *syn* isomer. A mixed P/N ligand (Table 2, entry 2) essentially shut down the reaction, while monodentate phosphine ligands (Table 2, entries 3 and 4) gave moderate yields of **2a**

and poor *dr*. Bidentate phosphines gave both higher yields and *dr* (Table 2, entries 5–11), although correlations with typical ligand features, such as bite angle, sterics, or electronics, were not obvious. Intriguingly, dppm (Table 2, entry 11) gave the best balance of yield and *dr* and was chosen as the optimal ligand (see the Supporting Information for other ligands).

With an optimal set of conditions in hand, the scope was explored (Table 3, conditions A) and compared to Au(I) catalysis (conditions B).[5,10] Linear C5 alkyl groups (Table 3, entries 1 and 3) gave the cyclopentenes **2b**,**c** in moderate yields and low *dr* favoring the *syn* isomer with Pd. While branching in the C5 *i*Pr group of **1d** gave *anti*-**2d** in 6.5:1 *dr* using an Au(I) catalyst (conditions B), the *dr* was reversed to favor *syn*-**2d** in poor *dr* using Pd. C2 alkyl substitution in **1e** (Table 3, entries 7 and 8) enabled stereodivergence in the installation of the vicinal C1/C5 stereocenters.

While dialkyl substitution on the distal C5 allene carbon of **1f** was tolerated (Table 3, entries 9 and 10) to furnish **2f**, yields and *syn*/*anti* ratios were low. Alkyl substitution at the proximal C3 allene carbon of **1g** (Table 3, entries 11 and 12) delivered cyclopentene **2g** in approximately 1:1 *dr*, irrespective of whether Pd or Au catalysis was employed.As substitution on the allene is further increased in **1h**, Au(I) catalysts failed to promote cycloisomerization (Table 3, entry 14) to **2h**, whereas Pd (Table 3, entry 15) was successful. Another noteworthy difference between the performance of Au vs. Pd catalysts is the lack of reactivity in Au-catalyzed cycloisomerization of a terminal allene (Table 3, entry 16). In contrast, when **1i** was subjected to optimized Pd conditions (Table 3, entry 13), **2i** was obtained in 60% yield suggesting that competing isomerization to the 1,3-diene is not operative.[11]

Finally, *gem*-dimethyl substitution in the tether of **1a** gave both good yields and tunable *dr* in the products **2a**, depending in the catalyst that was employed (Table 3, entries 17 and 18). Overall, the results in Table 3 indicate that substrate control over stereodivergent installation of the vicinal C1/C5 stereocenter is most effectively achieved when the allene is substituted at C5 with a relatively bulky group or contains additional substitution in the tether, including at C2 of **2e** or the adjacent carbon. Small groups at C5, dialkylsubstitution at C5, or the presence of a C3 allene substituent, gave essentially the same *dr* for both Pd and Au.

To better understand how the nature of the substrate and the catalyst influence stereochemical outcome, mechanisms for both the Pd- and Au-catalyzed reactions were proposed (Scheme 2). In the case of Pd (Scheme 2, A), initial deprotonation of the cyclic malonate **3a** results in a sodium enolate intermediate, followed by further coordination of the distal allene double bond[12] to the metal center yielding **3b**. C–C bond formation occurs via an outer-sphere carbopalladation[13] step that establishes the C1/C5 stereochemistry and forms vinyl Pd species **3c**. Protodepalladation is accomplished by MeOH, generated in the initial deprotonation step. The lack of reactivity in the absence of exogenous base argues against an allene hydropalladation/nucleophilic addition mechanism[3e,8] via insertion into the acidic C–H bond of the pronucleophile. Control experiments using only MeOH show no reaction, suggesting a hydropalladation/nucleophilic addition mechanism is also unlikely.

The origin of the observed diastereoselectivity using Pd catalysis is thought to arise from the buildup of $A^{1,3}$ strain in the transition state leading from **3b** to vinyl-Pd **3c**. When R^1 = alkyl and R^2 = H in intermediate **3b**, the rate of nucleophilic attack of the sodium enolate on the Pd–allene complex is hypothesized to exceed the rate of Pd-mediated allene epi merization, thus giving rise to an excess of the *syn* diastereomer **3c** (see Table 1, entry 1). When R^1 = H and R^2 = alkyl, Pd-mediated epimerization is expected to proceed faster than nucleophilic addition. In the case where R^1 and R^2 are both alkyl groups, the energetic and steric differences between the possible conformations of catalytic intermediate **3b** (Scheme 2, A) are presumed to be insignificant, thus resulting in almost equal mixtures of both *syn* and *anti* diastereomers (see Table 2, entry 9). Alternatively, coordination of **3a** by an Au(I) catalyst and the $Cu(OTf)_2$ additive results in a hypothesized η^1-π-allyl intermediate **3d**[5,14] (Scheme 2, B). When R^1 = alkyl and R^2 = H, the conformation shown in **3d** is thought to predominate, where steric interactions between R^2 and R^3 are minimized, thus giving rise to an excess of the *anti* **3e**, which undergoes rapid protodeauration by *in situ* generated triflic acid.[5] Efforts to further elucidate the structure of these proposed catalytic intermediates and refine the stereochemical outcome are being pursued in our laboratory.

In summary, complementary methods using Au(I) and Pd(0) catalysts to construct substituted cyclopentenes have been developed to favor *anti* or *syn* stereochemistry, respectively, from simple and easily obtained allene precursors.[15] Initial investigations into the mechanism of this transformation suggest a hydropalladation/nucleophilic addition mechanism is most likely not operative; mechanistic studies are ongoing to support the mechanism proposed in Scheme 2 (A). These methods allow access to highly substituted cyclopentenes with catalyst control of diastereoselectivity for a variety of lactone-containing allene substrates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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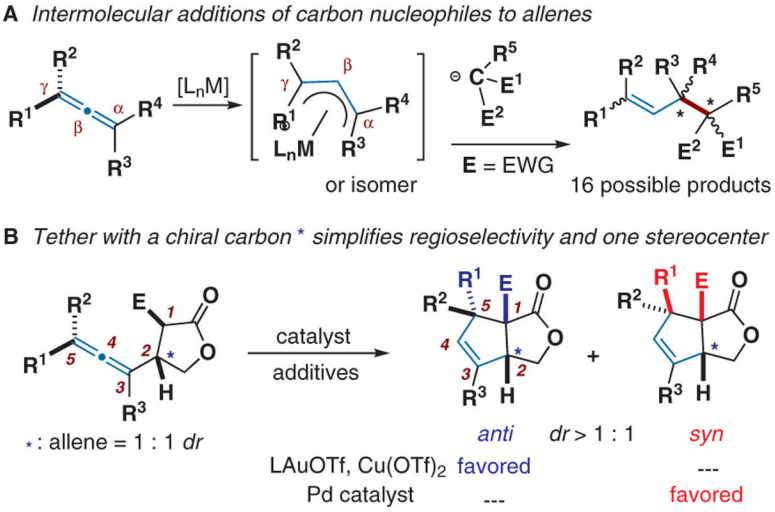
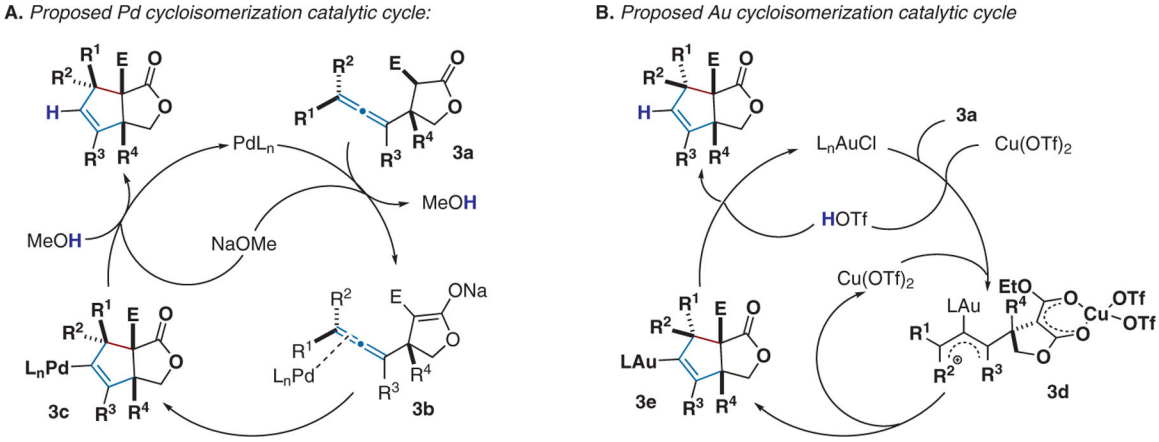
(15). Pd(0)-Catalyzed Cycloisomerization of Allenes – General ProcedureA flame-dried screw top vial was charged with Pd_2dba_3 (11.0 mg, 0.012 mmol, 0.05 equiv) and dppm (9.2 mg, 0.024 mmol, 0.10 equiv) in a glove box. The vial was sealed with a septum and removed from the glove box, and anhydrous THF (1.2 mL) was added. The resulting orange solution was stirred at room temperature under an N_2 atmosphere for 15 min before a solution of lactone **1h** (66.0 mg, 0.24 mmol, 1.00 equiv) in anhydrous THF (1.2 mL) was added, followed by the addition of NaOMe (15.2 mg, 0.28 mmol, 1.20 equiv). The septum was replaced with a screw top, and the resulting suspension was heated to 70 °C and stirred at this temperature for 12 h. After stirring was complete, the solution was cooled to room temperature and quenched by the addition of aqueous NH_4Cl (15 mL) and extracted with 3 × 15 mL portions of EtOAc. The combined organics were dried over Na_2SO_4 and the volatiles removed in vacuo to afford the crude cyclization products. The crude material was purified via flash column chromatography on silica gel using a gradient of 0–20% EtOAc in hexanes to give33.6 mg (0.12 mmol, 50% isolated yield) of cyclopentene **2h** as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ (major diastereomer) = 5.61 (dt, *J* = 3.1, 1.6 Hz, 1 H), 4.24 (d, *J* = 9.0 Hz, 1 H), 4.05 (d, *J* = 9.1 Hz, 1 H), 3.76 (s, 3 H), 3.16 (t, *J* = 6.9 Hz, 1 H), 1.95–1.85 (m, 1 H), 1.69 (t, *J* = 1.5 Hz, 3 H), 1.49–1.22 (m, overlapping signals, 7 H), 1.28 (s, 3 H), 0.89 (ddd, *J* = 8.7, 4.4, 2.1 Hz, 3 H); δ (minor diastereomer) = 5.41 (q, *J* = 1.7 Hz, 1 H), 4.27 (d, *J* = 9.0 Hz, 1 H), 3.94 (d, *J* = 9.0 Hz, 1 H), 3.79 (s, 3 H), 3.46 (dddd, *J* = 9.7, 5.8, 2.8, 1.8 Hz, 1 H), 1.86–1.76 (m, 1 H), 1.66 (dd, *J* = 2.7, 1.5 Hz, 3 H), 1.50–1.22 (m, overlapping signals, 7 H), 1.07 (s, 3 H), 0.89 (ddd, *J* = 8.8, 4.4, 2.1 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.0, 173.9, 169.0, 167.2, 140.1, 138.3, 130.3, 129.4, 72.5, 71.7,65.7, 65.3, 59.7, 57.6, 52.7, 52.3, 50.2, 47.8, 32.4, 31.9, 31.9, 29.1,28.6, 27.6, 22.6, 22.6, 17.7, 16.4, 14.1, 14.0, 11.9, 11.8. HRMS (ESI): *m/z* calcd for C_{16}H O + 24 4 [M + H] : 281.1747; found: 281.1744.$_{232}$**1h**$_{424}$**2h**$^1{}_3{}^{13}{}_{316}$



Scheme 1.

Inter- and intramolecular additions of carbon nucleophiles to allenes

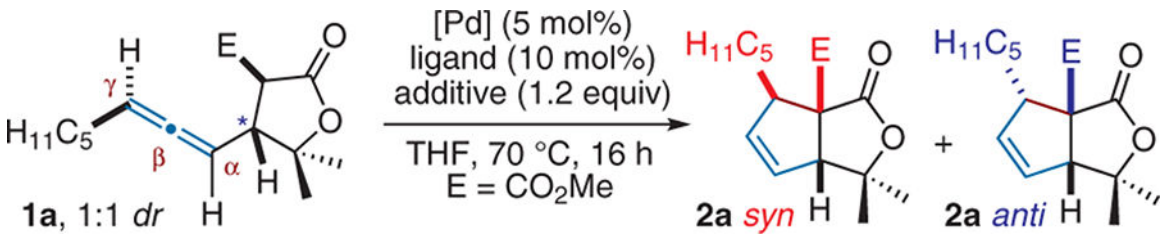


Scheme 2.

Proposed catalytic cycles for Pd- and Au-catalyzed allene cycloisomerizations

Table 1

Optimization of the Pd(0)-Catalyzed Allene Cycloisomerization



Entry	[Pd]	Ligand	Additive	Yield (%)[a]	dr[b]
1	(DTBM-SEGPHOS)PdOTf$_2$	dppe	Yb(OTf)$_3$/AcOH	0	-
2	Pd$_2$dba$_3$	dppe	AcOH	0[c]	-
3	Pd$_2$dba$_3$	dppm	-	0[c]	-
4	Pd$_2$dba$_3$	dppm	Cu(OTf)$_2$	15[c]	1.1:1
5	Pd$_2$dba$_3$	dppm	Et$_3$N	0[c]	-
6	Pd$_2$dba$_3$	dppm	*i*PrNEt	trace[c]	-
7	Pd$_2$dba$_3$	dppm	DBU	trace[c]	-
8	Pd$_2$dba$_3$	dppm	NaH	trace[c]	-
9	Pd$_2$dba$_3$	dppm	Na$_2$CO$_3$	0	-
10	Pd$_2$dba$_3$	dppm	K$_2$CO$_3$	24[c]	1:1
11	Pd$_2$dba$_3$	dppm	Cs$_2$CO$_3$	53	-
12	Pd(OAc)$_2$	dppe/LiBr	NaOMe	43	1.3:1
13	Pd$_2$dba$_3$	dppe	NaOMe	68	2.5:1

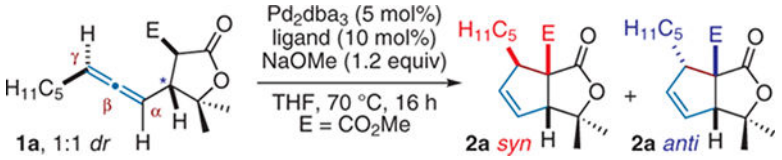
[a]NMR yield using mesitylene as internal standard.

[b]*syn*/*anti*.

[c]The major identifiable product results from isomerization of the allene **1a** to the 1,3-diene.

Table 2

Ligand Optimization Studies



Entry	Ligand	Yield (%)[a]	*dr*[b]
1	neocuproine	71	1.4:1
2	2,6-bis(*t*Bu$_2$MeP)py	trace[c]	-
3	PPh_3	56	1.4:1
4	PCy_3	47	1.4:1
5	dppf	63	2:1
6	dppp	39	4:1
7	dppbz	39	2.4:1
8	dppe	68	2.5:1
9	dCype	54	2.5:1
10	dCypm	49	1.8:1
11	dppm	77	3:1

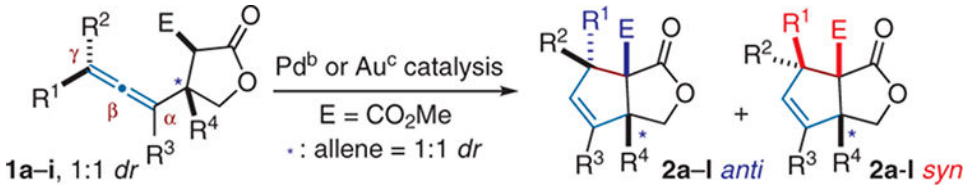
[a] NMR yield using mesitylene as internal standard.

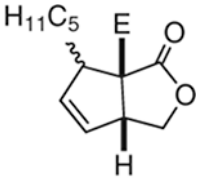
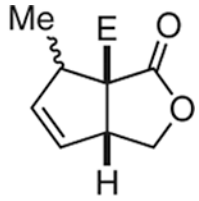
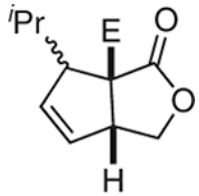
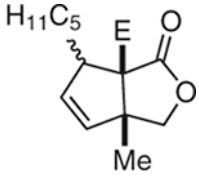
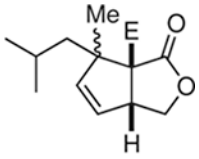
[b] *syn*/*anti*.

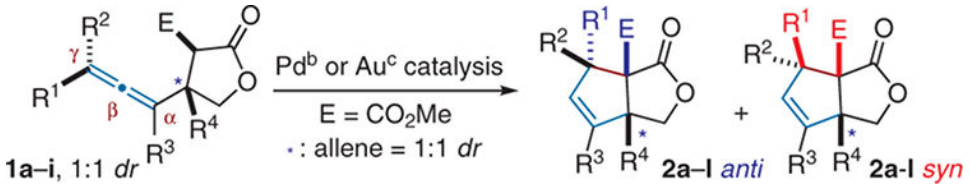
[c] The major identifiable product results from isomerization of the allene **1a** to the 1,3-diene.

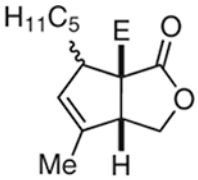
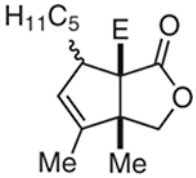
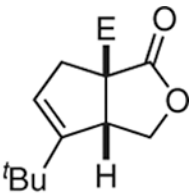
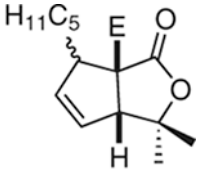
Table 3

Scope of Au- and Pd-Catalyzed Allene Cycloisomerization



Entry	Product	Conditions[a]	Yield (%)[b]	dr[c] (anti/syn)
1	 2b	A	54	1:2.0
2		B	93	1.8:1
3	 2c	A	83	1:1
4		B	60	1.2:1
5	 2d	A[e]	40	1:1.2
6		B (E = CO_2Et)	39	6.5:1
7	 2e	A[e] B	46	1:2.4
8		(E = CO_2Et)	54[c]	3.6.1
9	 2f	A[e]	37	1:1.3
10		B (E = CO_2Et)	27	1.1:1



Entry	Product	Conditions[a]	Yield (%)[b]	dr[c] (anti/syn)
11	 2g	A	48	1:1.2
12		B	30	1.4:1
13	 2h	A[e]	54	1:1.2
14		B	0	-
15	 2i	A	60	-
16		B	0	-
17	 2a	A	77	1:3
18		B	89	6.6:1

[a] Conditions A: [Pd] conditions: Pd_2dba_3 (5 mol%), dppm (10 mol%), NaOMe (1.2 equiv), THF, reflux, 12 h. Conditions B: [Au] conditions: Cy_3PAuCl (2.5 mol%), $Cu(OTf)_2$ (25 mol%), toluene, reflux, 24 h (see ref. 5 for additional details).

[b] 1H NMR yield with mesitylene as internal standard.

[c] *anti*/*syn*.

[d] Isolated yield.

[e] Sealed vial.