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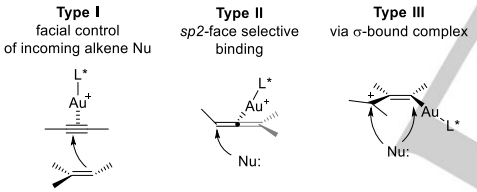
Asymmetric Synthesis of Dihydropyranones via Au(I)-Catalyzed Intermolecular [4+2] Annulation of Propiolates and Alkenes

Hanbyul Kim,[a] Su Yeon Choi[a] and Seunghoon Shin*[a]

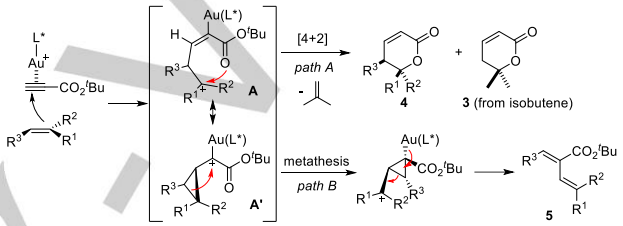
Abstract: Intermolecular asymmetric gold catalysis involving alkyne activation presents a significant challenge, due to its distinct mechanistic mode from other metals. Herein, we report a highly enantioselective synthesis of α,β-unsaturated δ-lactones from [4+2] annulation of propiolates and alkenes in upto 95% ee. Notably, for the desired chiral recognition, the choice of 1,1,2,2-tetrachloroethane as solvent was found to be crucial. Furthermore, an anionic surfactant (SDS) improved the product selectivity in the divergence of the cyclopropyl gold carbene intermediate.

α,β-Unsaturated δ-lactone scaffolds are found in a number of medicinal compounds displaying an array of significant biological activities.[1],[2] Their stereoselective assembly commonly employs multistep sequences comprised of allylation/acylation/RCM or hetero Diels-Alder/oxidation,[3] and more recently, organocatalytic [4+2] annulations via azolium dienolates have also been documented.[4] Based on the powerful alkynophilic activation in gold(I) catalysis,[5] we have demonstrated that the dihydropyranones could be assembled in a single step from an intermolecular [4+2] annulation of propiolates with alkenes.[6] However, achieving high level of enantiocontrol has remained elusive in this class of intermolecular gold(I)-catalyzed coupling.



Scheme 1. Types of enantio-determining steps in intermolecular asymmetric Au(I) catalysis.

Gold(I) complexes, having a linear coordination geometry[7] are reluctant to undergo metallacyclopentene formation or insertion of π-bonds[8] that occur in a close vicinity of chiral ligands. Instead, the enantio-determining step in gold(I)-catalysis involves discrimination of prochiral faces of an alkene nucleophile, approaching away from the linearly coordinated Au(L*) complex (Type I, Scheme 1). In fact, asymmetric gold(I) catalysis based on the alkyne activation has been realized only in intramolecular 1,n-enyne cycloisomerizations,[9] before a recent breakthrough in the intermolecular [2+2] annulation was reported by Echavarren and coworkers.[10] Despite remarkable advances in asymmetric Au(I) catalysis,[11] most of successful intermolecular reactions have involved either face-selective activation of alkenes/allenes by Au(I) (Type II)[12] or σ-bound Au(I) intermediates (Type III)[13-17] in the enantio-determining step, where chiral recognition occurs much closer to L*. In intermolecular Type I reactions, a ligand-controlled asymmetry on the prochiral nucleophiles has so far been notoriously challenging to achieve. Herein, we report a successful intermolecular [4+2] annulation of propiolates using diverse alkenes, leading to α,β-unsaturated δ-lactones in upto 95% ee.



Scheme 2. Product selectivity in the proposed mechanism: [4+2] annulation vs. enyne cross metathesis.

In addition to the enantiocontrol in the formation of **4** (path A, Scheme 2), the proposed mechanism for the [4+2] annulation presents additional product selectivity issues. Depending on the olefin types, 1,2-disubstituted olefins with electronically similar alkyl groups favor metathesis pathway to **5** (path B).[6] In addition, isobutene generated from the *tert*-butyl propiolate[18] can be more nucleophilic than some alkenes, leading to **3**. Based on this, we set out to examine the reaction of 2-Me-2-butene **2a** as an olefin partner (Table 1). Using 2.5 mol% of (*R*)-DM-segphos(AuCl)$_2$/AgSbF$_6$ (1:1) in 1,2-Cl$_2$-ethane, **4a** was obtained in 57% yield with 70% ee and careful inspection of the reaction mixture revealed competitive formation of metathesis product **5a** (31%) as well as conjugate addition adduct **6a** (10%) (entry 1). In an effort to optimize the enantio- as well as product selectivity, we initiated a search for the optimal ligand scaffold. Unfortunately, however, extensive screening of privileged bisphosphine ligands, such as Biphep, Garphos, Binap, Synphos, and Josiphos as well as fine-tuning the Ar groups in Segphos series, returned only inferior enantioselectivity to (*R*)-DM-Segphos. Various monophosphine or phosphite ligands were also tested, only to give almost racemic **4a** (see Table S2 for a complete ligand test).[19] Assuming that the recognition of alkenes by the cationic gold-alkyne complex is critically influenced by the solvents, various solvents and anions were then tested (entries 2-9). To our delight, use of 1,1,2,2-tetrachloroethane (TCE) gave significantly improved selectivity (entry 4). Surprisingly, addition of sodium dodecyl sulfate (SDS) in an equimolar amount to dimeric gold complex led to a significant reduction of **5a** and **6a**, along with an increase in enantioselectivity (84% yield, 85% ee, entries 10-12 vs. entry 9). The chain length of the surfactant also mattered since the addition of sodium ethyl sulfate made no difference from its

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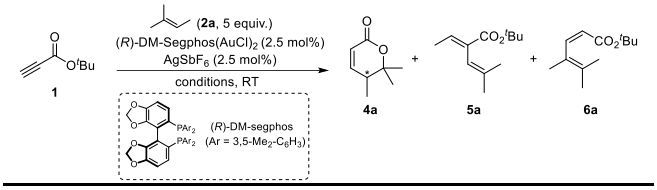
Table 1. Optimization of reaction conditions.[a]

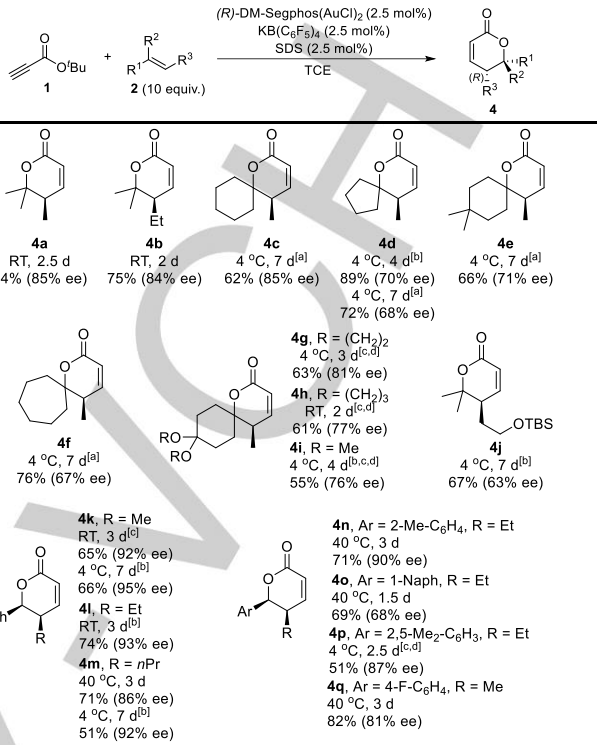


Entry	Conditions	Yields (%) (**4a**/**5a**/**6a**)	ee (%)
1	DCE, 11 h	57//31/10	70
2	1,1-Cl_2-ethane, 18 h	51/ND[b]	75
3	1,2,3-Cl_3-propane, 18 h	50/14/6	73
4	1,1,2,2-Cl_4-ethane (TCE), 24 h	50/ ND[b]	80
5	$C_6H_5CF_3$, 40 h	54/19/11	71
6	C_6H_5Cl, 24 h	68/14/14	45
7	*o*-Cl_2-C_6H_4, 24 h	58/23/14	76
8	TCE, $AgNTf_2$,[c] 12 h	70/24/6	77
9[d]	TCE, $KB(C_6F_5)_4$,[c] 24 h	57/32/8	81
10[d]	TCE, $KB(C_6F_5)_4$,[c] 1% SDS, 2.5 d	70/21/8	84
11[d]	TCE, $KB(C_6F_5)_4$,[c] 2.5% SDS, 2.5 d	84/12/4	85
12[d]	TCE, $KB(C_6F_5)_4$,[c] 5% SDS, 2.5 d	70/21/6	84
13[d]	TCE, $KB(C_6F_5)_4$,[c] 2.5% $EtOSO_3Na$, 2.5 d	64/27/6	82
14[d]	TCE, $KB(C_6F_5)_4$,[c] 2.5% $nC_{18}H_{37}OSO_3Na$, 3 d	77/17/4	83
15[d]	TCE, $KB(C_6F_5)_4$,[c] 2.5%Triton X-100, 3 d	NR	-

[a] Propiolates (0.25 M), **2** (5 equiv.) in the presence of *in-situ* formed Au(I)-catalyst, if not otherwise mentioned; isolated yields of **4a/5a/6a**. [b] **5a** and **6a** were not detected, but unidentified side products formed. [c] $AgNTf_2$ instead of $AgSbF_6$. [d] 10 equiv. of **2a**

absence (entries 13-14). In contrast, neutral (entry 15), zwitter-ionic or cationic surfactant had detrimental effect on the conversion (see Table S7 for additional surfactant screening).[19] Despite improved control of product selectivity, however, the reactions with SDS additive were slower, most likely due to its competitive coordination with the cationic gold(I), saturating the coordination site for olefins. The control of product selectivity by anionic surfactant *in organic solvent* was surprising.[20] Based on the ^{31}P NMR in combination with the mass spectrometric analysis (Figures S1-S8), we hypothesized that the sulfate anion resides in the vicinity of cationic Au(I) complex (Scheme S1),[21] forming a hydrophobic nano-environment for tighter interaction with alkenes. Thus, the desired [4+2] pathway (path A, Scheme 2), having a more negative $\Delta S^{\ddagger}$, would be favored over competing rearrangement into metathesis **5** (path B) or conjugate addition **6**.

Table 2. Reactions with tri-substituted and 1,2-di-substituted styryl alkenes.



Modification of conditions from the reaction arrow: [a] 5 equiv. of alkenes. [b] 5 mol % each of $L(AuCl)_2$/halogen abstractor/SDS (if any). [c] Absence of SDS. [d] $AgNTf_2$ instead of $KB(C_6F_5)_4$.

On the bases of the above optimization study, we examined the generality of the olefin scope in the [4+2] annulation (Table 2). Initially, tri-substituted aliphatic alkenes leading to lactones **4a-4j** having a single stereogenic center at C5 were tested. For **2a**-**2f**, $KB(C_6F_5)_4$ gave higher enantioselectivity than $AgNTf_2$, although the reaction with the latter was faster. Exo-cyclic olefins **2c-f** allowed the use of 5 equiv. of olefins but required a lower temperature for enantioselectivity. The carbophilic Lewis acidity of Au(I) allowed incorporation of acetals and silyl ethers as in **2g-j**. For **2g-i**, $KB(C_6F_5)_4$ as an anion source significantly slowed down the conversion (<30% yield), and $AgNTf_2$ gave acceptable yields with 76-81% ee. We then moved on to styryl 1,2-di-substituted alkenes (*Z*)-**2k-q** (Z/E >99:1). To our delight, (*Z*)-**2k** delivered 65% of *cis*-**4k** in 92% ee (a single diastereomer), which was improved to 95% ee using 5 mol% of (*R*)-DM-segphos$(AuCl)_2$ at 4 °C. Variously substituted styryl olefins **4l-q** also provided satisfactory enantioselectivity (81-93% ee, except **4o**), as their single respective diastereomers.

Tri-substituted aliphatic olefins (*Z*)- or (*E*)-**2r-2zb** that generate two stereogenic centers turned out to be excellent substrates as well (Table 3). With 5 equiv. of **2** and 2.5 mol% (*R*)-DM-segphos$(AuCl)_2$, these olefins afforded uniformly high enantioselectivity in reasonable yields. For aliphatic tri-sibstituted olefins **2r**-**2t**, higher enantioselectivity was obtained with $B(C_6F_5)_4$ anion, while, for aryl bearing **2u**-**2za**, NTf_2 anion gave higher enantioselectivities. In all cases, (*Z*) and (*E*)-**2** proceeded stereospecifically into *cis*- and *trans*-**4**, respectively, with minimal erosion of diastereoselectivity. This indicates that intramolecular

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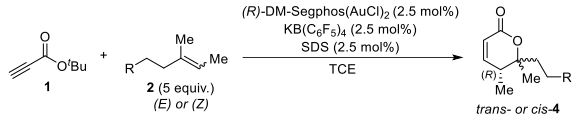
Table 3. Diastereospecific reactions with (*Z*)- or (*E*)-trisubstituted olefins.

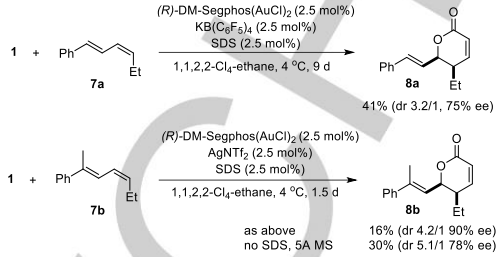


entry	R	(*Z*)- or (*E*)-**2**	conditions	Yield (%) (dr)[a]	ee (%)
1	H	(*Z*)-**2r** (1:>99)	4 °C, 7d[b]	66 (>1/99)	88
2		(*E*)-**2r** (>99:1)	4 °C, 7d	76 (>99/1)	81
3	^{n}Hex	(*Z*)-**2s** (3:97)	RT, 2.5d	70 (4/96)	83
4		(*E*)-**2s** (>99:1)	4 °C, 4.5d[c]	66 (95:5)	77
5	*c*-Hex	(*Z*)-**2t** (1:>99)	RT, 2.5d	55 (6/94)	83
6		(*E*)-**2t** (>99:1)	RT, 2.5d	72 (>99/1)	72
7	Ph	(*Z*)-**2u** (5:95)	4 °C, 1.5d[c]	78 (5/95)	84
8		(*E*)-**2u**(>99:1)	4 °C, 1.5d[c]	69 (94/6)	86
9	2-Me-C_6H_4	(*Z*)-**2v** (5:95)	4 °C, 2d[c]	70 (7/93)	80
10		(*E*)-**2v** (>99:1)	4 °C, 2.5d[c]	70 (97/3)	85
11	3-Me-C_6H_4	(*Z*)-**2w** (6:94)	4 °C, 2.5d[c,d]	69 (9/91)	83
12		(*E*)-**2w** (>99:1)	4 °C, 3d[c,d]	60 (97/3)	84
13	4-Me-C_6H_4	(*Z*)-**2x** (5:95)	4 °C, 3d[c,d]	69 (6/94)	85
14		(*E*)-**2x** (>99:1)	4 °C, 3.5d[c]	61 (95/5)	87
15	4-MeO-C_6H_4	(*Z*)-**2y** (7:93)	4 °C, 3d[c,d]	77 (9/91)	86
16		(*E*)-**2y** (>99:1)	4 °C, 3d[c,d]	68 (97/3)	89
17	4-Cl-C_6H_4	(*Z*)-**2z** (7:93)	4 °C, 2d[c]	68 (9/91)	89
18		(*E*)-**2z** (>99:1)	4 °C, 3d[c,d]	60 (95/5)	88
19	2-Naph	(*Z*)-**2za** (5:95)	4 °C, 2d[c]	60 (5/95)	89
20		(*E*)-**2za** (>99:1)	4 °C, 2.5d[c]	58 (>99/1)	87
21	AcO-$(CH_2)_3$	(*Z*)-**2zb** (10:90)	RT, 24 h[c]	81 (10/90)	83

Modification of conditions from the reaction arrow: [a] *trans/cis* ratio of **4**. [b] 5 mol% each of $L(AuCl)_2$/halogen abstractor/SDS (if any). [c] $AgNTf_2$ instead of $KB(C_6F_5)_4$. [d] Absence of SDS;

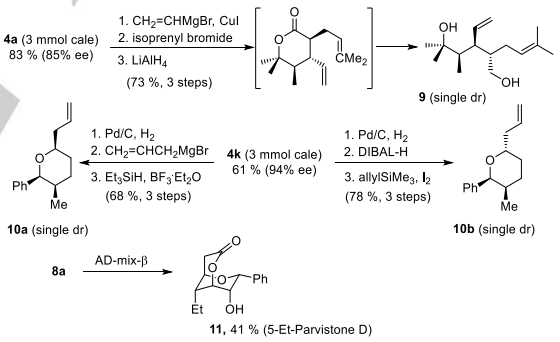
trapping of intermediate **A** by the carboxylate (Scheme 2) is faster than the rotation of C-C bond. Generally, use of SDS led to cleaner reactions and higher product selectivity, and, for some substrates (entries 11-13, 15-16, and 18), lowering temperature had similarly beneficial entropy effect to SDS. The optical purity of **4k** and *trans*-**4za** could be increased to >99% ee after a single recrystallization and their absolute stereochemistry was determined by X-ray crystallography to be (*R*) at C5 in both, from which stereochemistry of other products was inferred.[22]

Several olefins remained as limitations to the current methods. For example, 1,1-disubstituted alkenes afforded nearly racemic products. According to our proposed mechanism (path A, Scheme 2) these olefins do not generate a stereogenic center during the formation of cyclopropyl gold carbene **A/A'** (enantio-determining step) and absence of R^3 in **A** would facilitate free C-C rotation leading to racemic products. (*E*)-1,2-Disubstituted and mono-substituted styryl olefins gave lower % ee (<40% ee).



Scheme 3. [4+2] annulation with 1,3-dienes.

Finally, 1,3-dienes **7a-b** were considered as nucleophilic olefins (Scheme 3). The corresponding products would give a C5-Et analog of goniothalamin and potential intermediates for the synthesis of fostriecin family of natural products.[3a,23] However, dienes were especially challenging substrates and typically generated extensive oligomerization and epimerization.[24] Notwithstanding this, the reaction of **7a** ((*E,Z*)/(*E,E*)>99:1) delivered **8a** in 75% ee (dr 3.2/1), where the desired product was obtained in accord with Markovnikov selectivity. **7b** ((*E,Z*)/(*E,E*) = 90:10) could also be transformed into **8b** with upto 90% ee, despite a low yield.



Scheme 4. Synthetic applications of products

Synthetically, the α,β-unsaturated δ-lactones served as an outstanding platform for vicinal stereocontrol, as exemplified in the conversion of **4a** (prepared in 3 mmol scale) into highly decorated diol **9** as a single diastereomer. Dihydropyranone **4k** (prepared in 3 mmol scale) could be converted either into *cis*-**10a** or *trans*-**10b** tetrahydropyrans in highly diastereoselective fashion. In addition, Sharpless asymmetric dihydroxylation of **8a** provided 5-Et analog of parvistone D in only two steps from the diene **7a**.

In conclusion, we have demonstrated that intermolecular Au(I)-catalyzed [4+2] annulation from *t*-butyl propiolate and alkenes in a highly enantioselective fashion (upto 95% ee). Various alkenes including tri-substituted as well as (*Z*)-1,2-disubstituted styryl olefins functioned as effective nucleophilic partners. The challenge of enantio-control involving a linearly

coordinated alkyne-Au(I) complex could be addressed with the use of 1,1,2,2-tetrachloroethane as solvent. Furthermore, the use of an anionic surfactant (SDS) in organic solvents provided improved product selectivity that may be applicable in other catalysis involving cationic metal/π-complexes.

Acknowledgements

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Keywords: asymmetric gold catalysis • intermolecular alkyne activation • α,β-unsaturated δ-lactones • SDS • entropy control

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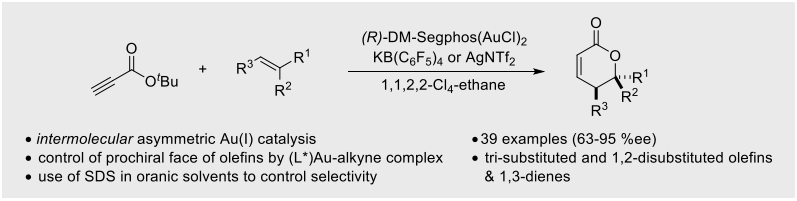

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Page No. – Page No.

Asymmetric Synthesis of Dihydropyranones via Au(I)-Catalyzed Intermolecular [4+2] Annulation of Propiolates and Alkenes

Enantioselective [4+2] annulation of propiolates with alkenes led to the synthesis of dihydropyranones in upto 95% ee. This one-step protocol provides an efficient route to α,β-unsaturated δ-lactone scaffolds from di-, tri-substituted alkenes as well as 1,3-dienes.