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Asymmetric Synthesis of Allenyl Oxindoles and Spirooxindoles via Catalytic Enantioselective Saucy-Marbet Claisen Rearrangement

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asymmetric catalysis; Claisen rearrangement; allenyl silane; oxindole; spirooxindole

The development of catalytic enantioselective Claisen rearrangement reactions is a longstanding challenge in organic synthesis.^[i] Only five highly enantioselective catalytic versions of this concerted rearrangement have been reported in the more than 100 years since this reaction was discovered, relying on Lewis acids,^[ii–iii] hydrogen bonding catalysts^[iv] or chiral *N*-heterocyclic carbenes.^[v] A related asymmetric transformation via a π -allyl intermediate has also been reported.^[vi] Furthermore, enantioselective catalysis in the rearrangements of alkynyl vinyl ethers has not been described, even though auxiliary controlled diastereoselective versions are documented.^[vii] In asymmetric catalysis, such a reaction presents a distinct set of challenges since the alkyne *sp* centers distort the transition state geometries and the cylindrically symmetric alkyne provides no opportunity for facial discrimination. In addition, the allenyl products of such a rearrangement are poised to undergo tandem reactions to rapidly generate complex structures. We report here the first asymmetric catalytic Saucy-Marbet Claisen rearrangement, the transformation of propargyl ethers to provide β -substituted allenyl carbonyls (Scheme 1).^[viii] The reaction gives rise to two classes of chiral oxindoles containing newly formed quaternary centers: allenyl compounds and spirocyclic lactones via a tandem rearrangement.

To start, we employed propargyl substituted indoles (**3**) which were obtained readily from **1** and **2** (Scheme 1).^[ix] The oxindole products (**4**) of the subsequent Saucy-Marbet Claisen rearrangement are central building blocks in the construction of indole alkaloids^[x] and are attractive platforms for pharmaceutical agents.^[xi] For these reasons, the development of catalytic asymmetric methods for their generation has been the subject of much research.^[3,xii] In particular, the formation of enantiopure oxindoles with allenyl substitution at C3 has not been reported.

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Evaluation of **3a** with representative hydrogen bonding and Lewis acid catalysts^[xiii] revealed that the rearrangement occurred readily. Beginning with Pd complexes,^[iii] we were disappointed with the poor selectivity (Table 1, entries 1–3) seen with the methyl ester **3a–c** using *t*-BuPHOX catalysts (Chart 1). Not unexpectedly, the alkyne geometry significantly alters the topology of the rearrangement transition state (Scheme 2). Closer inspection of proposed stereochemical models revealed that the ester group, which undergoes a gearing effect from the catalyst, would interact with larger alkyne terminal substituents to destabilize the less favorable reaction pathway. In line with this hypothesis, very high levels of enantioselection (96–98% ee) were observed with alkynes having *ortho*-substituted aryls at R² along with rapid conversions (8 h at –15 °C) at 5 mol% catalyst loading (Table 1, entries 4–7). However, alkynes with other larger groups such as trimethylsilyl, *tert*-butyl, or MIDA boronate^[xiv] were less successful (entries 8–10).

Due to the poor results with non-aryl alkynes, additional ligands (**6–8**, Chart 1) were examined. A stereochemical model with BINAP (see Supporting Information) revealed the potential for good stereodifferentiation, which was borne out with the larger *tert*-butyl-substituted substrate (Table 2, entry 3), but not the smaller congeners (entries 1–2). Screening of other metal catalysts demonstrated that only the Pd complexes possessed an adequate combination of reactivity and selectivity (see Supporting Information). Further optimization around BINAP ligand framework proved that difluoroPHOS was the most effective providing *tert*-butyl-substituted allene **4i** with 90% yield and 86% ee (Table 2, entry 4 vs entries 3 and 5). Surprisingly, use of the TMS-substituted alkyne with the optimal DifluoroPHOS complexes provided poor selectivity (Table 2, entry 6). Hypothesizing that trace fluoride may arise from the DifluoroPHOS, a return to BINAP (Table 2, entry 7) proved effective. Unfortunately, with 20 mol% of the Pd complex (entry 8), the enantioselectivity suffered even after optimization of the solvent. Use of larger silyl groups (TES, TBS) allowed the selectivity to be retained even under catalytic conditions (entries 9–10). Good to excellent enantioselectivities were obtained in the rearrangement of a range of different indole cores producing the TES- or TBS-substituted allenes (entries 9–15) with as little as 5 mol% catalyst (entry 12). The absolute configurations of the products were established through crystal structures and are in accord with the proposed stereochemical models (Scheme 2 and Supporting Information).

In attempting to use catalytic amounts of the palladium complex with much larger TIPS substrates, higher temperatures (40 °C vs rt) were required which also caused the formation of spirocyclic lactone **9q** in addition to allene **4q** (Scheme 3 and Table 3, entry 1). Hypothesizing that trace water together with Pd catalyst hydrated the allene **4** to form intermediate ketone **A** (Scheme 3), 2,4,6-tris-*tert*-butylpyridine was introduced. In accord with this premise, the additive suppressed formation of the spirocyclic lactone and cleanly produced allene with up to 89% ee (Table 3, entries 2–3) using the SEGPHOS ligand (**7b**). Alternatively, (TMEDA)Zn(SbF₆)₂ was found to selectively absorb water improving selectivity to 94% ee (entry 4). Notably, the allene and spiro lactone products were quite stable, for example, stirring with 0.25 equiv of TFA in CH₂Cl₂ overnight at ambient temperature caused no decomposition.

The potential clinical significance of spirocyclic oxindoles^[xv] has led to a demand for efficient methods for their enantioselective synthesis.^[xvi] In addition to their presence in a large number of biologically active natural products,^[xvii] their topology allows functionalization of all four faces of a tetrahedron centered on the spirocyclic center, creating an ideal environment for structural diversity. For these reasons, the tandem formation of spirocyclic lactone **9** warranted further study. Isolation of TES-substituted allene **4k** (90% *ee*) and TIPS-substituted **4q** (89% *ee*) followed by resubjection to the reaction conditions resulted in conversion to **9k** (90% *ee*) and **9q** (89% *ee*), respectively. Furthermore, the α -silylketone **A** (Scheme 3) from the TBS-substituted alkyne **3m** was isolated and found to cyclize to the spirocyclic lactone in the presence of the palladium catalyst. From these results, we propose a mechanism involving palladium-catalyzed allene hydration to form **A** followed by palladium-catalyzed cyclization (Scheme 3). Consistent with this mechanism, addition of a small amount of water (5–10 mol%) provided spiro lactone products **9** in one step with high efficiency (Table 3, entries 5–13). In particular, this class of compounds is difficult to prepare with only a two examples reported^[ix,xviii] for the synthesis of the racemic, saturated versions of these spirooxindoles. With our method, substrates with different esters or indole substituents were well tolerated, providing the spirooxindoles with good yields and enantioselectivities (Table 3, entries 5–13). Reactions conducted on a larger scale also proceeded well (Table 3, entry 5). A key component of this mechanism is stabilization of the carbocationic intermediate **B** via the β -silyl effect;^[xix] indeed, non-silyl substrates reluctantly formed the spiro lactone, resulting in a mixture of rearrangement product **4** and intermediate **A**.

A further study of the mechanism of the formation of allene **4** from **3** was undertaken by reacting two different substrates in the same flask (Scheme 4). The lack of any crossover of the alkyne portion points to a concerted Saucy-Marbet Claisen rearrangement rather than a stepwise ionic mechanism.

The allenyl products **4** of the Saucy-Marbet Claisen rearrangement were found to be useful substrates for a number of transformations (Scheme 5), in addition to the formation of the spiro lactone (see above). For example, protodesilylation of **4k** readily provided the simplest congener **4a**, which was not directly accessible with high selectivity via the rearrangement (see entry 1 in Tables 1 and 2). Hydration of the allene also occurred readily with $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ providing α -silyl ketone **10** which could be further induced to undergo Brook rearrangement to silyl enol ether **11**.

In summary, the first catalytic, enantioselective Claisen rearrangement utilizing alkynyl substrates has been developed. This concerted Saucy-Marbet Claisen rearrangement constitutes a mild entry to a range of allenyl oxindoles bearing a quaternary stereocenter. In addition, tandem reactions of silyl-substituted substrates permit rapid assembly of complex spirooxindoles, an important class of biological active structures, in one operation. In addition, this discovery provides promise for the general use of alkynyl vinyl ethers in catalytic, asymmetric rearrangement reactions providing an alternative avenue to valuable allenes.

Experimental Section

(*R*)-Ethyl 3-(1-(*tert*-butyldimethylsilyl)propa-1,2-dien-1-yl)-5-methoxy-2-oxoindoline-3-carboxylate (**4n**)

To a solution of the Pd[(*R*)-BINAP](SbF₆)₂ complex (12 mg, 0.01 mmol, 20 mol%) in C₆H₅Cl (1 mL) was added a solution of **3n** (19.4 mg, 0.05 mmol) in toluene (1 mL) at ambient temperature. The resulting solution was stirred in the absence of light at room temperature until the starting material was completely consumed, as determined by TLC. Filtration through a plug of SiO₂ (5 mm × 2 cm) with ethyl ether, concentration of the solution and purification by column chromatography using 50% ethyl ether/hexane afforded **4n** as a white solid in 82% yield: mp 136–137 °C;

[α]_D²³ +158.18 (c 0.17, 93% *ee* CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.92 (bs, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.79–6.74 (m, 2H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.22 (qd, *J* = 7.5, 11.0 Hz, 1H), 4.13 (qd, *J* = 7.5, 11.0 Hz, 1H), 3.78 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 212.5, 174.8, 168.8, 155.7, 134.3, 129.7, 114.5, 113.2, 110.2, 100.2, 93.6, 74.1, 62.4, 56.1, 27.6, 19.4, 14.2, –4.0, –4.2; IR (film) 3252, 2958, 2858, 1931, 1746, 1622, 1468, 1259, 1089, 1027 cm^{–1}; HRMS (ES) *m/z* = 386.1788 calcd for C₂₁H₂₈NO₄Si [M-H][–], found 386.1776; CSP HPLC (Chiralpak IA, 1 mL/min, 95:5 hexanes: *i*-PrOH) t_R(1) = 14.0 min, t_R(2) = 21.6 min.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Saucy-Marbet Claisen rearrangement

Scheme 2.
Stereochemical model of the rearrangement.

Scheme 3.
Tandem formation of a spirocyclic oxindole

Scheme 4.
Crossover mechanism experiment

Scheme 5.

Transformations of the allenyl oxindoles

Chart 1.
Bidentate ligands

Table 1

[*t*-BuPHOX]Pd(SbF₆)₂-Catalyzed Saucy-Marbet Rearrangement (Scheme 1)^[a]

Entry	3	R ¹	R ²	mol% cat	T (°C)	t	Yield (%)	ee (%)
1	a	Me	H	20	0	10 min	100 ^[b]	14
2	b	Me	Me	20	0	15 min	100 ^[b]	45
3	c	Me	Ph	5	0	8 h	96	78
4	d	Me	<i>o</i> -MePh	5	-15	8 h	95	98
5	e	Me	<i>o</i> -BrPh	5	-15	8 h	93	96
6	f	Me	1-Nap	5	-15	8 h	95	98
7	g	Me	<i>o</i> -MeOPh	5	-15	8 h	90	98
8	h	Me	TMS	20	0	90 min	15	14
9	i	Me	<i>t</i> -Bu	20	0	2 d	100 ^[b]	45
10 ^[c]	j	Me	MIDA-B ^[d]	20	45	2 d	60	70

^[a] Reaction conditions: 0.025 M, [*t*-BuPHOX]*Pd(SbF₆)₂, CH₂Cl₂.

^[b] Conversion (%).

^[c] 1:5:5 MeCN:C₆H₅Cl:CH₂Cl₂.

^[d] MIDA boronate, see reference 13.

Table 2

Substrate Scope in the Oxindole Rearrangement (Scheme 1)^[a]

Entry	L	3	R ¹	R ²	R ³	mol% cat	t	Yield (%)	ee (%)
1	6	a	Me	H	H	20	10 min	100	8
2	6	b	Me	Me	H	20	30 min	100	4
3	6	i	Me	<i>i</i> -Bu	H	20	2 d	40	76
4	7a	i	Me	<i>i</i> -Bu	H	100	10 h	90	86
5	8	i	Me	<i>i</i> -Bu	H	100	10 h	90	83
6	7a	h	Me	TMS	H	100	10 h	95	44
7	6	h	Me	TMS	H	100	4 h	90	77
8	6	h	Me	TMS	H	20	4 d	100	60
9	6	k	Me	TES	H	20	6 d	78	90
10	6	l	Me	TBS	H	20	5 d	90	89
11	6	m	Et	TBS	7-Me	20	5 d	87	90
12	6	m	Et	TBS	7-Me	5	10 d	76	90
13	6	n	Et	TBS	5-OMe	20	5 d	82	93
14	6	o	Et	TBS	7-OMe	20	6 d	91	93
15	6	p	Et	TBS	5-Br	20	6 d	85	90

^[a] Reaction Conditions: L*Pd(SbF₆)₂, 0.025 M CH₂Cl₂ at 0 °C. With TES, TBS substrates: 1:1 C₆H₅Cl:C₆H₅CH₃ at rt.

Table 3

Tandem Rearrangement-Spirocyclization (Scheme 3)^[a]

Entry	3	R ¹	R ²	R ³	t (d)	Solvent ^[b]	Yield (%)		ee (%)	
							4	9	4	9
1	q	Me	TIPS	H	4.5	A	23	62	89	90
2 ^[c]	q	Me	TIPS	H	10	A	80		82	
3 ^[c,d]	q	Me	TIPS	H	10	A	61		89	
4 ^[e]	q	Me	TIPS	H	4.5	A	55		94	
5 ^[f]	q	Me	TIPS	H	4.5	C		78 ^[g]		90
6 ^[f]	r	Et	TIPS	H	4	C		95		90
7 ^[f]	s	CH ₂ CF ₃	TIPS	H	4	C		90		87
8 ^[f]	t	Bn	TIPS	H	4	C		95		92
9 ^[f]	u	Et	TIPS	7-Me	6	B		93		96
10 ^[f]	v	Et	TIPS	5-OMe	5	A		81		91
11 ^[f]	w	Et	TIPS	7-OMe	6	C		90		92
12 ^[f]	x	Et	TIPS	5-Br	6	B		82		92
13 ^[f,h]	l	Me	TBS	H	5	B		95		86

^[a] Reaction Conditions: 0.025 M, 20 mol% [BINAP]Pd(SbF₆)₂, 40 °C.

^[b] Solvents: A) CH₂Cl₂, B) 1:1 C₆H₅Cl:C₆H₅CH₃, C) C₆H₅Cl.

^[c] 30 mol% L*Pd(SbF₆)₂, 10 mol% 2,4,6-tris-*tert*-butylpyridine.

^[d] Ligand **7b** used.

^[e] 30 mol% L*Pd(SbF₆)₂, 10 mol% (TMEDA)/Zn(SbF₆)₂.

^[f] 5–10 mol% H₂O added.

^[g] Performed with 0.5 mmol substrate.

^[h] Reaction conducted at rt.