Asymmetric Catalysis

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Asymmetric Synthesis of Allenyl Oxindoles and Spirooxindoles by a Catalytic Enantioselective Saucy–Marbet Claisen Rearrangement**

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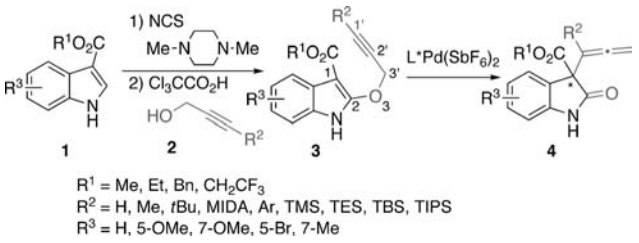
The development of catalytic enantioselective Claisen rearrangement reactions is a longstanding challenge in organic synthesis.[1] In the more than 100 years since the reaction was discovered, only five highly enantioselective catalytic versions of this concerted rearrangement have been reported; these reactions rely on either Lewis acids,[2,3] hydrogen-bonding catalysts[4] or chiral N-heterocyclic carbenes.[5] A related asymmetric transformation via a π-allyl intermediate has also been reported.[6] Furthermore, enantioselective catalysis in the rearrangements of alkynyl vinyl ethers has not been described, even though auxiliary-controlled diastereoselective versions are documented.[7] 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. Herein we present the first catalytic asymmetric Saucy–Marbet Claisen rearrangement, namely the transformation of propargyl ethers to provide β-substituted allenyl carbonyls (Scheme 1).[8] The reaction gives rise to two classes of chiral oxindoles containing newly formed quaternary centers: allenyl compounds and spirocylic lactones through a tandem rearrangement.



Scheme 1. Saucy–Marbet Claisen rearrangement. NCS = *N*-chlorosuccinimide, MIDA = *N*-methyliminodiacetic acid, TMS = trimethylsilyl, TES = triethylsilyl, TBS = *tert*-butylsilyl, TIPS = triisopropylsilyl.

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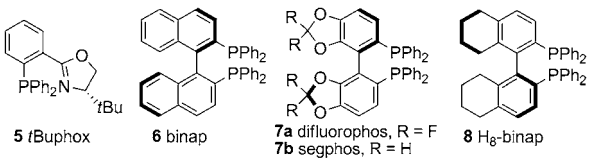
To start, we employed propargyl-substituted indoles **3**, which were readily obtained from **1** and **2** (Scheme 1).[9] The oxindole products **4** of the subsequent Saucy–Marbet Claisen rearrangement are central building blocks for the construction of indole alkaloids[10] and are attractive platforms for pharmaceutical agents.[11] For these reasons, the development of catalytic asymmetric methods for their generation has been the subject of much research.[3,12,13] In particular, the formation of enantiopure oxindoles with allenyl substitution at C3 has not yet been reported.

Evaluation of **3a** with representative hydrogen bonding and Lewis acid catalysts[14] revealed that the rearrangement readily occurred. However, when we began testing Pd complexes,[3] we were disappointed with the poor selectivity (Table 1, entries 1–3) seen with the methyl ester **3a–c** using catalysts based on the *t*Buphox ligand (Scheme 2). Not unexpectedly, the alkyne geometry significantly alters the topology of the rearrangement transition state (Scheme 3). 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

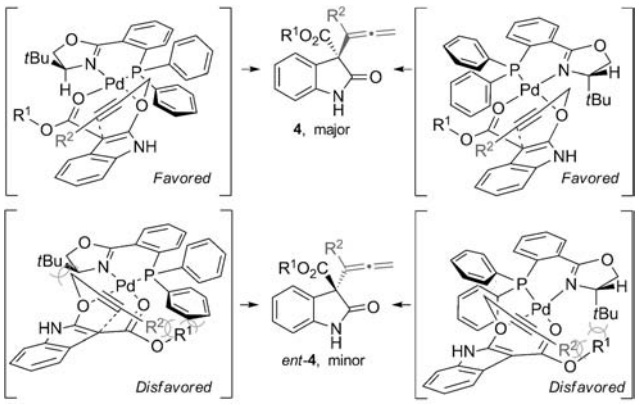
Table 1: (*t*Buphox)Pd$(SbF_6)_2$-catalyzed Saucy–Marbet rearrangement (Scheme 1).[a]

Entry	3	R^1	R^2	cat. [mol%]	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	*o*-Tol	5	−15	8 h	95	98
5	**e**	Me	*o*-BrC_6H_4	5	−15	8 h	93	96
6	**f**	Me	1-Nap	5	−15	8 h	95	98
7	**g**	Me	*o*-MeO C_6H_4	5	−15	8 h	90	98
8	**h**	Me	TMS	20	0	90 min	15	14
9	**i**	Me	*t*Bu	20	0	2 days	100[b]	45
10[c]	**j**	Me	MIDA-B[d]	20	45	2 days	60	70

[a] Reaction conditions: (*t*Buphox)*Pd$(SbF_6)_2$ (0.025 M), CH_2Cl_2. [b] Conversion [%]. [c] 1:5:5 MeCN/C_6H_5Cl/CH_2Cl_2. [d] MIDA boronate; see reference [13]. Nap = naphthyl, TMS = trimethylsilyl, MIDA = *N*-methyliminodiacetic acid.



Scheme 2. Bidentate ligands used.



Scheme 3. Stereochemical model of the rearrangement.

pathway. In line with this hypothesis, very high levels of enantioselection (96–98% *ee*) were observed with alkynes having *ortho*-substituted aryl groups at R^2, along with rapid conversions (8 h at −15 °C) at 5 mol% catalyst loading (Table 1, entries 4–7). However, alkynes with larger groups, such as trimethylsilyl (TMS), *tert*-butyl, or *N*-methyliminodiacetic acid (MIDA) boronate,[15] were less successful (entries 8–10).

Owing to the poor results with non-aryl alkynes, additional ligands (**6–8**, Scheme 2) 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 and 2). Screening of other metal catalysts demonstrated that only the palladium complexes possessed an adequate combination of reactivity and selectivity (see Supporting Information). Further optimization around the 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 gave poor selectivity (Table 2, entry 6). Hypothesizing that trace fluoride may arise from the difluorophos, we returned to binap (Table 2, entry 7), which proved effective. Unfortunately, with 20 mol% of the Pd complex (entry 8), the enantioselectivity suffered even after optimization of the solvent. The use of larger silyl groups, such as triethylsilyl (TES) or *tert*-butylsilyl (TBS), allowed the selectivity to be retained even under catalytic conditions (entries 9 and 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 X-ray crystallography and are in accord with the proposed stereochemical models (Scheme 3; see also the Supporting Information).

In attempting to use catalytic amounts of the palladium complex with much larger triisopropylsilyl (TIPS) substrates, higher temperatures (40 °C vs. RT) were required, which also caused the formation of spirocyclic lactone **9q** along with allene **4q** (Table 3, entry 1 and Scheme 4). Hypothesizing that trace water together with the Pd catalyst hydrated allene **4** to form intermediate ketone **A** (Scheme 4), we tried adding

Table 2: Substrate scope in the oxindole rearrangement (Scheme 1).[a]

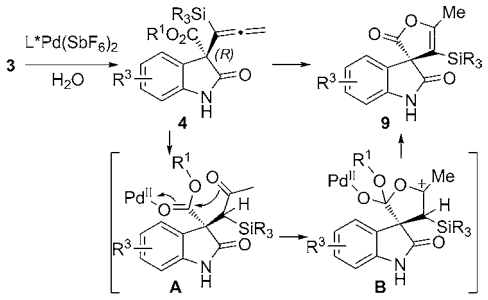
Entry	L	3	R^1	R^2	R^3	cat. [mol%]	*t*	Yield [%]	*ee* [%]
1	**6**	**a**	Me	H	H	20	10 min	100	8
2	**6**	**b**	Me	Me	H	20	30 min	100	4
3	**6**	**i**	Me	*t*Bu	H	20	2 days	40	76
4	**7a**	**i**	Me	*t*Bu	H	100	10 h	90	86
5	**8**	**i**	Me	*t*Bu	H	100	10 h	90	83
6	**7a**	**h**	Me	TMS	H	100	10 h	95	44
7	**6**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

[a] Reaction conditions: L*Pd$(SbF_6)_2$ (0.025 M), CH_2Cl_2 at 0 °C. With TES, TBS substrates: 1:1 $C_6H_5Cl/C_6H_5CH_3$ at RT. TMS = trimethylsilyl, TES = triethylsilyl, TBS = *tert*-butylsilyl.

Table 3: Tandem rearrangement–spirocyclization (Scheme 4).[a]

Entry	3	R^1	R^2	R^3	*t* [days]	Solvent[b]	Yield [%] 4	Yield [%] 9	*ee* [%] 4	*ee* [%] 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_2CF_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: (binap)Pd$(SbF_6)_2$ (0.025 M, 20 mol%), 40 °C. [b] Solvents: A) CH_2Cl_2, B) 1:1 $C_6H_5Cl/C_6H_5CH_3$, C) C_6H_5Cl. [c] 30 mol% L*Pd$(SbF_6)_2$, 2,4,6-tris-*tert*-butylpyridine (10 mol%). [d] Ligand **7b** used. [e] 30 mol% L*Pd$(SbF_6)_2$, (tmeda)Zn$(SbF_6)_2$ (10 mol%). [f] 5–10 mol% H_2O added. [g] Performed with 0.5 mmol substrate. [h] Reaction conducted at RT. TIPS = triisopropylsilyl, TBS = *tert*-butylsilyl.

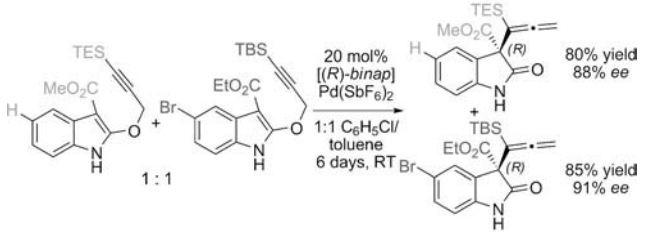


Scheme 4. Tandem formation of a spirocyclic oxindole.

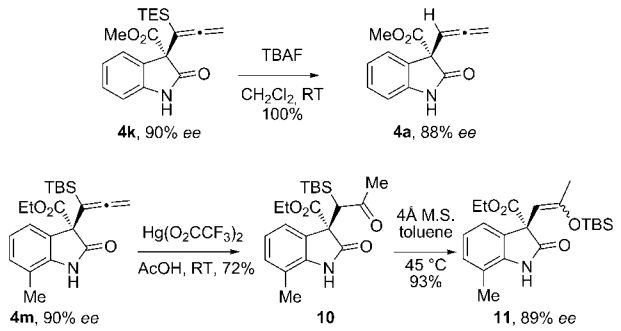
2,4,6-tris-*tert*-butylpyridine. In accord with this premise, the additive suppressed formation of the spirocyclic lactone and cleanly produced the allene with up to 89% *ee* (Table 3, entries 2 and 3) using the segphos ligand (**7b**). Alternatively, $(tmeda)Zn(SbF_6)_2$ was found to selectively absorb water, improving selectivity to 94% *ee* (entry 4; tmeda = tetramethylethylenediamine). Notably, the allene and spirolactone products were quite stable; for example, stirring with 0.25 equiv of trifluoroacetic acid in CH_2Cl_2 overnight at ambient temperature caused no decomposition.

The potential clinical significance of spirocyclic oxindoles[16] has led to a demand for efficient methods for their enantioselective synthesis.[17,18] Apart from their presence in a large number of biologically active natural products,[19] 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 4) 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 4). Consistent with this mechanism, addition of a small amount of water (5–10 mol%) provided spirolactone products **9** in one step with high efficiency (Table 3, entries 5–13). This class of compounds is particularly difficult to prepare, with only two examples reported[9,20] 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** through the β-silyl effect;[21] indeed, non-silyl substrates reluctantly formed the spirolactone, resulting in a mixture of rearrangement product **4** and intermediate **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 5). The lack of any crossover of the alkyne portion points to a concerted Saucy–Marbet Claisen rearrangement rather than a stepwise ionic mechanism.



Scheme 5. Crossover mechanism experiment.



Scheme 6. Transformations of the allenyl oxindoles. TBAF = tetrabutylammonium fluoride, M.S. = molecular sieves.

The allenyl products **4** of the Saucy–Marbet Claisen rearrangement were found to be useful substrates for a number of transformations (Scheme 6), in addition to the formation of the spirolactone (see above). For example, protodesilation of **4k** readily provided the simplest congener **4a**, which was not directly accessible with high selectivity by the rearrangement (see entry 1 in Tables 1 and 2). Hydration of the allene also readily occurred with $Hg(O_2CCF_3)_2$ providing α-silyl ketone **10**, which could be further induced to undergo a Brook rearrangement to provide 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. Furthermore, tandem reactions of silyl-substituted substrates permit the rapid assembly of complex spirooxindoles, an important class of biologically active structures, in one operation. Moreover, this discovery provides promise for the general use of alkynyl vinyl ethers in catalytic, asymmetric rearrangement reactions, providing an alternative route to valuable allenes.

Experimental Section

(*R*)-Ethyl 3-(1-(*tert*-butyldimethylsilyl)propa-1,2-dien-1-yl)-5-methoxy-2-oxoindoline-3-carboxylate (**4n**): A solution of **3n** (19.4 mg, 0.05 mmol) in toluene (1 mL) was added to a solution of the Pd[(*R*)-binap]$(SbF_6)_2$ complex (12 mg, 0.01 mmol, 20 mol%) in C_6H_5Cl (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 SiO_2 (5 mm × 2 cm) with diethyl ether, concentration of the filtrate, and purification by column chromatography using 50% diethyl ether/hexanes afforded **4n** as a white solid in 82% yield: mp 136–137 °C; $[\alpha]_D^{23} = +158.18$ ($c = 0.17$, 93% *ee*, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.92$ (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 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 212.5$, 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 ppm; IR (film) $\tilde{\nu} = 3252$, 2958, 2858, 1931, 1746, 1622, 1468, 1259, 1089, 1027 cm^{-1}; HRMS (ES) $m/z = 386.1788$ calcd for $C_{21}H_{28}NO_4Si$ $[M-H]^-$, found 386.1776; CSP HPLC (Chiralpak IA, 1 mL min^{-1}, 95:5 hexanes/*i*PrOH) $t_R(1) = 14.0$ min, $t_R(2) = 21.6$ min.

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