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Catalytic Enantioselective Meerwein−Eschenmoser Claisen Rearrangement: Asymmetric Synthesis of Allyl Oxindoles

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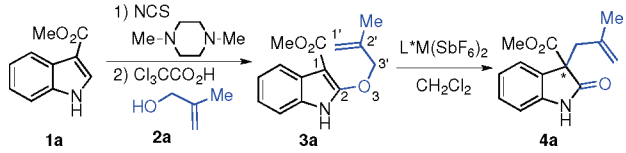
The [3,3′] sigmatropic rearrangements of allyl vinyl ethers (Claisen rearrangement) and their derivatives have enjoyed a long and rich history due to the utility of the products.[1] Though first discovered almost 100 years ago, only one substrate class has proven amenable to asymmetric catalysis.[2] The 2-ester substituted allyl vinyl ethers undergo highly enantioselective rearrangement with both Lewis acid[3] and hydrogen bonding[4] catalysts. A key barrier to development of this transformation is identification of systems that turn over readily with catalysts.[5] We have discovered that allyloxy-indoles are another class of substrates that permit turnover. Using palladium complexes, we report here the first asymmetric catalytic Meerwein−Eschenmoser Claisen rearrangement.

The Meerwein−Eschenmoser Claisen rearrangement involves the transformation of 2-amino allyl vinyl ethers to γ,δ-unsaturated amides.[6] Typically, the formation of the intermediate hemiaminal requires forcing conditions rendering such processes unsuitable for asymmetric catalysis. While the formation of Claisen substrates with the vinyl portion in the aromatic ring is much more facile, rearrangement is more difficult because of the high activation energies accompanying dearomatization. The use of an indole-containing substrate (Scheme 1) allows the requisite intermediate **3a** to be constructed under mild conditions and gives rise to a facile rearrangement to **4a** at low temperature (ambient in the presence of silica).[7]

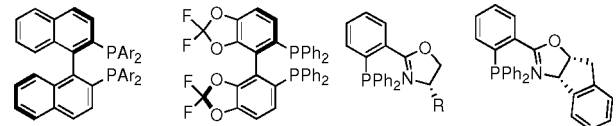
Scheme 1. Meerwein−Eschenmoser Claisen Rearrangement



Oxindoles such as **4a** are central building blocks in the construction of indole alkaloids[8] and are attractive platforms for the generation of pharmaceutical agents.[9] As a consequence, much effort has been devoted to the development of catalytic asymmetric methods for their construction.[10,11,8a,12,13] Even so, the formation of oxindoles with allyl and ester substitution at C3 or substitution in the aromatic framework remains a challenge.

Formation of **3a** as illustrated in Scheme 1 was straightforward; however, isolation in pure form proved difficult since **3a** spontaneously rearranges at low temperatures (room temp−40 °C). With careful control of the isolation protocol, **3a** could be isolated in pure form and stored for one year at −20 °C. Evaluation of **3a** with representative hydrogen bonding and Lewis acid catalysts revealed that the rearrangement occurred readily. In contrast to reported work with the 2-ester allyl vinyl ethers,[3,4] copper catalysts provided good enantioselection but poor turnover, whereas hydrogen-bonding catalysts provided good turnover but poor enantioselectivity.[14] On this basis, further metal catalysts were selected that undergo weaker coordination with the β-amidoester of **4a** to facilitate release of the product. While zinc, nickel, and silver catalysts were ineffective,[14] palladium catalysts possessed the necessary combination of substrate/product affinity and effective chiral environment. The optimal ligand sets for turnover were found to be the bisphosphines and phosphinooxazolines (PHOX)[15] (Table 1). For substrate **3a**, the *t*-BuPHOX (**7d**) palladium catalyst was superior providing **4a** with excellent yield and high enantioselectivity (entry 11, 89% ee). The counterion was crucial in line with catalyst coordination to the substrate β-amidoester array; the SbF_6 and BF_4 complexes provided faster rates and greater turnover than the corresponding perchlorates, triflates, and halides.

Table 1. Metal-Catalyzed Rearrangement (Scheme 1, **3a** to **4a**).



5a BINAP, Ar = Ph
5b tol-BINAP, Ar = 4-MeC_6H_4
5c xyl-BINAP, Ar = 3,5-$Me_2C_6H_3$

6 DifluoroPHOS

7a PhPHOX
7b BnPHOX
7c *i*-PrPHOX
7d *t*-BuPHOX

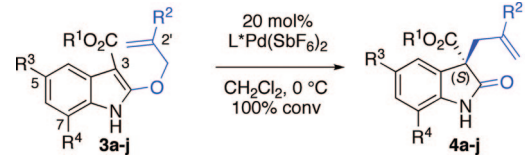
8 IndPHOX

entry	M	L*	mol %	*t*	convn (%)	ee (%)
1	–	–		5 h	0	NA
2	$AgSbF_6$	–	35	5 h	0	NA
3	$Pd(SbF_6)_2$	**5a**	100	50 min	100	48 (*S*)
4	$Pd(SbF_6)_2$	**5b**	100	20 min	100	47 (*S*)
5	$Pd(SbF_6)_2$	**5c**	100	20 min	100	50 (*S*)
6	$Pd(SbF_6)_2$	**6**	100	75 min	100	56 (*S*)
7	$Pd(SbF_6)_2$	**7a**	20	25 min	100	49 (*S*)
8	$Pd(SbF_6)_2$	**8**	20	20 min	100	72 (*S*)
9	$Pd(SbF_6)_2$	**7b**	20	10 min	100	48 (*S*)
10	$Pd(SbF_6)_2$	**7c**	20	5 min	100	73 (*S*)
11	$Pd(SbF_6)_2$	**7d**	20	20 min	100	89 (*S*)

[a] Reaction conditions: 0.025 M, CH_2Cl_2, 0 °C.

Good to excellent enantioselectivities were obtained in the rearrangement of a range of substrates (Table 2). The reactions were very fast, occurring within 5−30 min at 0 °C.[16] Optimal rates and enantioselectivities were observed in CH_2Cl_2 and no catalysis was observed in ethereal solvents such as Et_2O or THF.

For the bisphosphine (**5, 6**) derived catalysts, the enantioselectivity steadily increased as the size of the C3 ester group increased (Table 2, entries 2, 4−7) with the *tert*-butyl ester providing 89% ee with BINAP and 92% ee with a smaller dihedral angle ligand, difluoroPHOS.[17] On the other hand, sterically larger groups at the allyl C2′ position eroded selectivity (Table 2, entries 1, 3, 8). The PHOX series proved complemen-



(1)

10.1021/ja807026z CCC: $40.75

Table 2. Substrate Scope in the Oxindole Rearrangement (eq 1)[a]

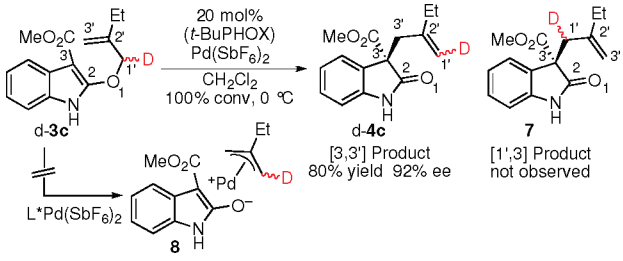
entry	L*	3/4	R^1	R^2	R^3	R^4	*t* (min)	yield (%)	ee (%)
1	**5a**	a	Me	Me	H	H	105	97	45
2	**5a**	b	Me	H	H	H	15	75	71
3	**5a**	c	Me	Et	H	H	50	70	35
4	**5a**	d	Bn	H	H	H	35	74	72
5	**5a**	e	*i*-Pr	H	H	H	40	91	74
6	**5a**	f	*t*-Bu	H	H	H	15	85	89[c]
7	**6**	**f**	**t-Bu**	**H**	**H**	**H**	**15**	**60**	**92**
8	**5a**	g	*t*-Bu	Me	H	H	10	82	82[c]
9	**5a**	**g**	***t*-Bu**	**Me**	**H**	**H**	**30**	**77**	**82**[c,d]
10	**7d**	**a**	**Me**	**Me**	**H**	**H**	**20**	**89**	**89 (91)**[b]
11	**7d**	a	Me	Me	H	H	20	100	88[c,d]
12	**7d**	b	Me	H	H	H	10	100	83
13	**7d**	**c**	**Me**	**Et**	**H**	**H**	**20**	**82**	**92**
14	**7d**	g	*t*-Bu	Me	H	H	20	73	58
15	**7d**	**h**	**Me**	**Me**	**OMe**	**H**	**20**	**60**	**91**
16	**7d**	**i**	**Me**	**Me**	**Br**	**H**	**20**	**82**	**87**
17	**7d**	**j**	**Me**	**Me**	**H**	**OMe**	**30**	**95**	**85**

[a] Reaction Conditions: 0.025 M **2**, 20 mol % L*Pd$(SbF_6)_2$, CH_2Cl_2, 0 °C. [b] Reaction performed on a 1 mmol scale with 95% yield. [c] Reaction performed at room temperature. [d] Run using 5 mol % L*Pd*$(SbF_6)_2$.

tary providing the best selectivity with the smaller C3 methyl ester and the larger C2′ groups (Table 2, entries 10−14). Notably, reactions conducted on a larger scale proceeded with slightly improved enantioselectivity (entry 10). Furthermore, high enantioselection was retained with either electron donating or electron withdrawing substitution on the aromatic ring (Table 2, entries 15−17). It was found that catalyst loadings could be lowered to 5 mol % with no loss in enantioselectivity (Table 2, entries 9, 11).

Because palladium(II) catalysts are employed here, the possibility of π-allyl cation chemistry (i.e., **8**) needed to be considered. On the basis of the results with other Lewis acids such as copper and zinc complexes (good to excellent enantioselectivity, but poor turnover), our preliminary hypothesis centers on a Lewis acid-catalyzed mechanism.[18] Further support for this pathway was found in the lack of any deuterium scrambling with labeled substrate *d*-**3c** (Scheme 2).

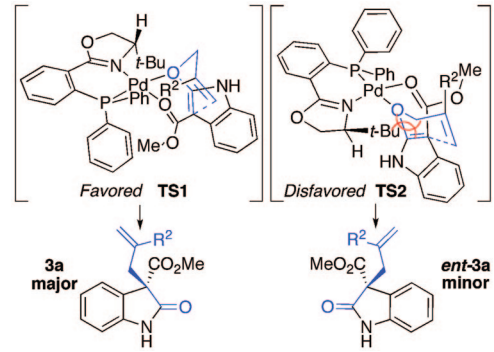
Scheme 2. Deuterium Labeling



The absolute configuration of the products was established through crystal structures of derivatives (see Supporting Information). Stereochemical models predicated on two-point coordination of the substrate β-amidoester moiety to a Lewis acidic palladium complex are in accord with the stereochemical outcomes for both the PHOX (Scheme 3) and bisphosphine catalysts. These models are also consistent with the selectivity trends of the different substrates described above. For example, larger ester groups destabilize **TS1** thereby leading to lower selectivity with the PHOX catalyst (Table 2, entry 10 vs 12).

In summary, the first catalytic, enantioselective Meerwein−Eschenmoser Claisen rearrangement has been developed. This method constitutes a mild entry to a range of oxindoles bearing a quaternary stereocenter. Future studies will focus on further optimization, as well expansion of the substrate scope.

Scheme 3. Stereochemical Model of the Rearrangement



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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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