Communication

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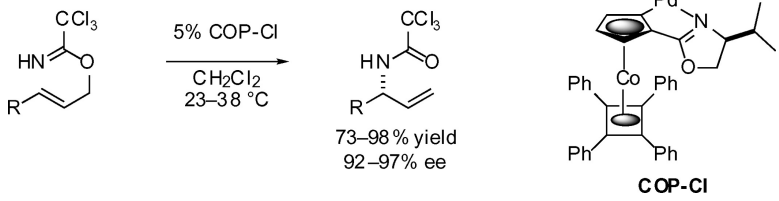
J. Am. Chem. Soc., **2003**, 125 (41), 12412-12413• DOI: 10.1021/ja037086r • Publication Date (Web): 19 September 2003



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Catalytic Asymmetric Rearrangement of Allylic Trichloroacetimidates. A Practical Method for Preparing Allylic Amines and Congeners of High Enantiomeric Purity

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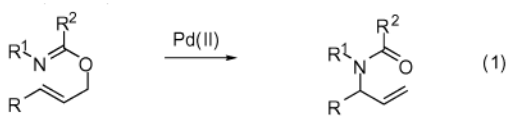
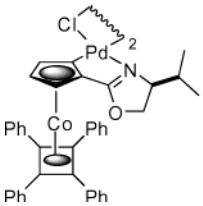
The rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides (**1** → **2**), first reported in 1974,[1] is the preferred method for converting allylic alcohols to transposed allylic amines and their derivatives.[2] This transformation can be accomplished at elevated temperatures or at room temperature in the presence of catalysts such as $Hg(OCOCF_3)_2$[1] or $PdCl_2$ complexes.[3] Attempts to date to develop asymmetric Pd(II) catalysts for the rearrangement of prochiral allylic trichloroacetimidates have been unsuccessful, being plagued by competing elimination reactions, slow reaction rates, and low enantioselectivities.[4] The first two of these difficulties likely arise from competitive complexation of the small, basic trichloroacetimidate nitrogen to palladium.[5] Consequently, success in developing asymmetric Pd(II) catalysts for allylic imidate rearrangements has been realized only with *N*-arylimidates (**3** → **4**).[4,6] As coordination of an imidate nitrogen to a neutral palladium



center should be less favorable than to a cationic Pd(II) complex, typically employed in asymmetric allylic imidate rearrangements,[4,6] the recent discovery that chloride-bridged dimer **5**[7] is an excellent catalyst for asymmetric rearrangement of *N*-(*p*-methoxyphenyl)-trifluoroacetimidates[6f] suggested that COP−Cl (**5**) might also catalyze allylic rearrangement of synthetically more important allylic trichloroacetimidates. In this Communication, we report that **5** is indeed an outstanding catalyst for transforming prochiral (*E*)-allylic trichloroacetimidates into allylic trichloroacetamides of high enantiopurity.



5 (COP-Cl)

The trichloroacetimidates employed in this study were prepared in 68−99% yield by DBU-catalyzed addition of allylic alcohols to trichloroacetonitrile.[8] Table 1 summarizes results obtained from catalytic rearrangements of nine representative primary allylic trichloroacetimidates with 5 mol % COP−Cl (**5**) in CH_2Cl_2 (0.6 M) for 18 h. (*E*)-Allylic trichloroacetimidates containing unbranched R substituents at C3 rearranged within 18 h at room temperature to provide the corresponding (*S*)-allylic trichloroacetamides **2** in

Table 1. Enantioselective Formation of Allylic Trichloroacetamides **2** from (*E*)- and (*Z*)-Allylic Trichloroacetimidates **1**[a]

		imidate			amide	
entry	cpds	R	*E*/*Z*	temp (°C)	yield (%)[b]	% ee[c]/conf
1	a	*n*-Pr	*E*	rt	80	94/*S*
2	a	*n*-Pr	*E*	38 °C	99	95/*S*
3	b	*n*-Pr	*Z*	38 °C	17	71/*R*
4	c	*i*-Bu	*E*	38 °C	95	96/*S*
5	c	*i*-Bu	*E*	38 °C[d]	92	98/*S*
6	d	*i*-Bu	*Z*	38 °C	8	73/*R*
7	e	Me	*E*	rt	85	92/*S*
8	f	Cy	*E*	38 °C[e]	82	96/*S*
9	g	CH_2CH_2Ph	*E*	rt	83	96/*S*
10	g	CH_2CH_2Ph	*E*	38 °C	93	93/*S*
11	h	Ph	*E*	rt	13	nd[f]
12	i	*t*-Bu	*E*	38 °C	7	nd[f]

[a] Conditions: 5 mol % catalyst **5**, CH_2Cl_2 (0.6 M), 18 h. [b] Duplicate experiments (±3%). [c] Determined by HPLC analysis of duplicate experiments (±2%). [d] 1 mol % **5**, CH_2Cl_2 (1.2 M). [e] CH_2Cl_2 (1.0 M). [f] nd = not determined.

92−96% ee and 80−85% yield (entries 1, 7, and 9); at 38 °C, yields of these rearrangements were improved (93−99%) with little or no erosion of enantioselection (entries 2 and 10). (*E*)-Allylic trichloroacetimidates containing *i*-Bu or cyclohexyl C3 substituents (**1c** and **1f**) rearranged slowly at room temperature; however, at 38 °C these precursors provided the corresponding (*S*)-allylic trichloroacetamides **2c** and **2f** in 96% ee and high yield (entries 4 and 8). When the substrate concentration was increased to 1.2 M, a catalyst loading of only 1 mol % could be employed, as demonstrated by the formation of **2c** in 92% yield and 98% ee (entry 5). The rearrangement was slowed drastically when R was *t*-Bu (entry 12). Also unreactive were (*Z*)-allylic trichloroacetimidates which gave the corresponding (*R*)-allylic trichloroacetamides **2** in poor yield and moderate enantioselectivity (entries 3 and 6). One additional limitation was identified: (*E*)-cinnamyl trichloroacetimidate **1h** provided amide **2h** in low yield with the major product resulting from formal [1,3]-rearrangement (entry 11).[9]

The rearrangement of a series of (*E*)-allylic trichloroacetimidates containing various Lewis basic substituents was examined to explore the functional group compatibility of the COP−Cl-catalyzed reaction (Table 2). Oxygen functionality (including ester, acetal, ketone, and silyl ether) was well tolerated, with allylic trichloroacetamide products being formed in 92−96% ee and excellent yield (entries 1−7). Trichloroacetimidate **1o** containing a free hydroxyl group rearranged in high yield in the presence of COP−Cl (entry 8); however, enantioselection in this case was lower (80% ee). Nitrogen functionality proved more problematic. Substrate **1p** containing carbamate functionality rearranged cleanly to give **2p** in 95% ee (96% yield at 38 °C), as did trichloroacetimidate **1q** containing a distal tertiary amine to provide **2q** in 97% ee (82% yield at 23 °C). However, the allylic rearrangement was prevented,

10.1021/ja037086r CCC: $25.00

Table 2. Enantioselective Synthesis of Allylic Trichloroacetamides **2** from (*E*)-Allylic Trichloroacetimidates **1** Containing Lewis Basic Functionality[a]

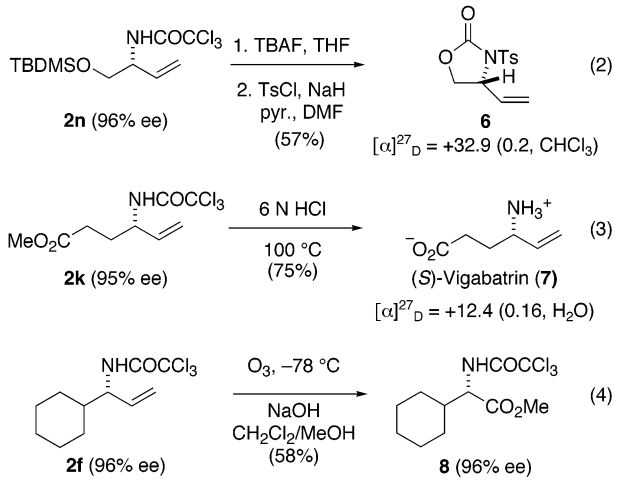
entry	cpds	R	temp (°C)	yield (%)[b]	% ee[c]/conf
1	j	$(CH_2)_3OAc$	rt	74	92/*S*
2	j	$(CH_2)_3OAc$	38 °C	97	92/*S*
3	k	$(CH_2)_2CO_2Me$	rt	73	95/*S*
4	l	$(CH_2)_3(OCH_2CH_2O)$	rt	85	95/*S*
5	m	$(CH_2)_2COMe$	rt	80	94[d]/*S*
6	m	$(CH_2)_2COMe$	38 °C	98	95[d]/*S*
7	n	$CH_2OTBDMS$	38 °C	98	96/*R*
8	o	CH_2OH	rt	84	80/*R*
9	p	$(CH_2)_3NBn(Boc)$	rt	87	95/*S*
10	p	$(CH_2)_3NBn(Boc)$	38 °C	96	95/*S*
11	q	$(CH_2)_9NBn_2$	rt	82	97/*S*

[a] Conditions: 5 mol % **5**, CH_2Cl_2 (0.6 M), 18 h. [b] Duplicate experiments (±3%). [c] Determined by HPLC analysis of duplicate experiments (±2%). [d] Determined by chiral GC analysis of duplicate experiments (±2%).

at least at 38 °C, by tertiary amine functionality at C6, secondary amine functionality at either C6 or C12, or a thioether substituent at C6 of the (*E*)-2-alkenyl trichloroacetimidate starting material.

As only (*E*)-allylic trichloroacetimidates are viable substrates in the COP−Cl-catalyzed allylic rearrangement, *ent*-COP−Cl (*ent*-**5**) was prepared to access the opposite enantiomer of allylic trichloroacetamide products.[10] Thus, rearrangement of crotyl trichloroacetimidate **1e** and 4-(*tert*-butyldimethylsiloxy)-2-butenyl-trichloroacetimidate (**1n**) with *ent*-**5** using conditions reported for these substrates in Tables 1 and 2, respectively, provided (*R*)-**2e** and (*R*)-**2n** in 92% ee (83% yield) and 96% ee (98% yield).

To illustrate the potential utility of enantioenriched allylic trichloroacetamide products, and establish the absolute configurations of **2n** and **2k**, the following transformations were carried out. Cleavage of the silyl protecting group of **2n** followed by tosylation provided (*R*)-*N*-tosyl-4-vinyloxazolidinone **6** of high enantiopurity (eq 2).[11] The GABA aminotransaminase inhibitor (*S*)-vigabatrin (**7**)[12] was readily prepared from **2k** by acidic cleavage of the trichloroacetyl and ester groups.[13] To illustrate the use of allylic trichloroacetamide products for enantioselective synthesis of unnatural α-amino acids, the double bond of **2f** was cleaved with ozone in basic methanol[14] to deliver the differentially protected (*S*)-α-amino ester **8** with no detectable loss of enantiomeric purity.[15,16]



In conclusion, COP−Cl (**5**) catalyzes the rearrangement of (*E*)-allylic trichloroacetimidates to provide transposed allylic trichloroacetamides in high yield and 92−98% ee, thus providing the first truly practical method for transforming prochiral allylic alcohols to enantioenriched allylic amines and their analogues. As (*E*)-allylic alcohols are readily available, their trichloroacetimidate derivatives are prepared in high yield from commercially available trichloroacetonitrile, oxidative removal of an *N*-aryl protecting group from the allylic amide product is not required, and the trichloroacetamide group can be easily cleaved or transformed to other functional arrays,[17] this catalytic asymmetric method for preparing chiral allylic amines and congeners should find considerable use in enantioselective synthesis.

Acknowledgment. We thank the NSF (CHE-9726471) for financial support, Drs. C. J. Richards and T. Remarchuk for useful discussions, and Dr. J. Ziller for X-ray analysis of **2e**. C.E.A. thanks Amgen for a predoctoral fellowship. NMR and mass spectra were determined at UCI with instruments purchased with the assistance of NSF and NIH shared instrumentation grants.

Note Added after ASAP. In the version published on the Web 9/19/2003, the structure for **2n**, **2k**, **2f**, and **8** in eqs 2-4 were incorrect. The version published 9/22/2003 and the print version are correct.

Supporting Information Available: Representative experimental procedures for trichloroacetimidate preparation and catalytic rearrangement, copies of HPLC and GC traces used to determine enantiopurity, and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA037086R