Oxidative Cyclization of Sulfamates Onto Pendant Alkenes

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Abstract

This communication discloses the first examples of *aza*-Wacker cyclizations of sulfamate esters. Within the realm of related cyclization reactions, this protocol is differential in that it forms 6-membered rings in good yield and uses catalytic amounts of palladium (0) rather than palladium (II) salts. These reactions scale well, and their products are demonstrated to be valuable synthetic intermediates.

Graphical Abstract
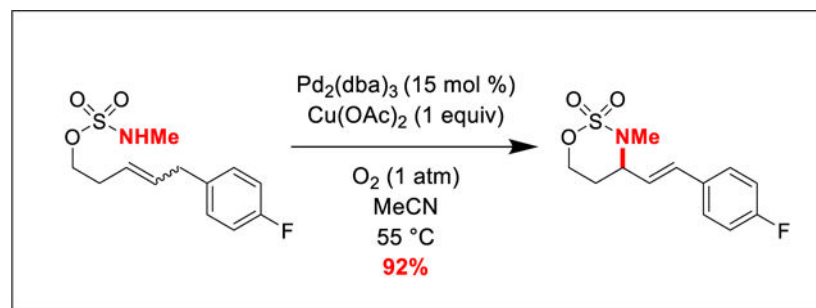
The oxidative functionalization of unsaturated moieties remains an area of vigorous research activity.[1–5] Within the realm of alkene functionalization, Wacker-type cyclizations of alcohols have been extensively investigated.[6–15] In sharp contrast, the analogous cyclization of nitrogen moieties onto alkenes, the *aza*-Wacker reaction, remains relatively under-explored.[16–18] Inspired by the pioneering studies of Åkermark, Bäckvall, Zetterberg[19–22] and Hegedus[23–25] as well as important recent contributions from Stoltz,[26] Zhang,[27–29] and Stahl,[30–34] among others,[35–41] we chose the *aza*-Wacker cyclization as a point of focus. Elegant aza-Wacker cyclization reactions have been disclosed with protected amines,[36, 37, 42] amides,[26, 28, 43] aminals,[35] and hemiaminals.[33] With few exceptions,[33, 44] the majority of these protocols have been developed with alkenyl amines and require the nitrogen functionality to be native to the molecule. Furthermore, examples of *aza*-Wacker protocols that form heterocyclic rings containing more than 5 atoms remain extremely

limited.[31, 37, 45–49] As the alcohol functional group is ubiquitous in organic molecules, a general protocol where a nitrogen containing auxiliary could be affixed to an alkenyl alcohol and then oxidatively cyclized would be highly desirable. We envisioned a reaction where diverse sulfamate auxiliaries would be easily appended to alcohols and then cyclized to form six-membered and larger rings in an *aza*-Wacker type process.[50–53]

In this communication, we disclose the first examples of *aza*-Wacker cyclizations of sulfamate esters. These reactions reliably yield valuable 6-membered oxathiazinane heterocycles with pendant unsaturation. The oxathiazinane moiety is a masked 1,3-amino alcohol, a motif found in myriad biologically active compounds (Figure 1), and can be used as a synthetic intermediate for a variety of transformations.[54–58] Our protocol, catalytic in palladium and reliant on $Cu(OAc)_2/O_2$ as stoichiometric oxidants, offers convenient access to these important synthetic intermediates (Scheme 1).

Optimization of an oxidative cyclization of alkenyl sulfamate esters was performed with (E)-hex-3-en-1-yl methylsulfamate **1a**, prepared in a single step from commercially available *trans*-3-hexen-1-ol (Table 1). Using Andersson's protocol for oxidative tosylamine cyclization $Pd(OAc)_2/O_2$ in DMSO, (See Supporting Information for reaction conditions),[36] the conversion of **1a** into **2a** was approximately 30%. While modest, this important result gave us hope that this reaction could be further developed. Augmenting these conditions with $Cu(OAc)_2$[59] boosted the yield of **2a** to 46% (Table 1, **Entry 1**). Switching solvents from DMSO to THF (Table 1, **Entry 2**), toluene (Table 1, **Entry 3**), or methanol (Table 1, **Entry 4**) was deleterious. In CH_3CN, the yield of **2a** was similar to that in DMSO (Table 1, **Entry 5**). Increasing the pressure of O_2 from 1 atm to 4 atm[31] did little (Table 1, **Entry 6**) to increase yield. Switching to palladium chloride salts was markedly deleterious (Table 1, **Entries 7–8**). In contrast to other *aza*-Wacker reactions, we saw no advantage with $Pd(TFA)_2$ relative to $Pd(OAc)_2$ (Table 1, **Entry 9**). Increasing the reaction temperature from 55 °C to 80 °C (Table 1, **Entry 10**) conferred a modest 5% boost in yield. At 55 °C, increasing the reaction time from 17 h to 26 h was similarly beneficial (Table 1, **Entry 11**). In conjunction with $Pd(OAc)_2$, bidentate ligands [$(PhSO)_2$, DPPE, bipyridine (Table 1, **Entry 12** and Supplementary Table 1)] and monodentate ligands [PPh_3, $P(OiPr)_3$, IMes, pyridine (Supplementary Table 1)] were invariably deleterious. To our great surprise, switching to catalytic $Pd_2(dba)_3$ (Table 1, **Entries 13–14**) improved the reaction yields dramatically. To our knowledge, this is the first disclosure of an aza-Wacker cyclization that employs a Pd(0) pre-catalyst.

Systematically varying the substituent attached to the sulfamate nitrogen (Table 2) revealed that the reaction is exquisitely sensitive to the steric bulk of alkyl substituents (Table 2, **Entries 1–4**). In contrast, diverse electron rich and electron deficient aryl substituents on the nitrogen are well tolerated (Table 2, **Entries 5–8**). We hypothesize that cis/trans isomerism in some of the products arises from reversible formation of a palladium π-allyl complex from the reaction of $Pd_2(dba)_3$ with the product oxathiazinanes.[60, 61] In the absence of any substituent on the nitrogen, the oxidative cyclization proceeded, albeit in lower yield than with alkyl or aryl substitution (Table 2, **Entry 9**). Such products are alternatively accessible via C-H amination processes[51, 62] and are not the focus of this study. Our protocol is complementary to C–H amination methods in that it allows convenient,

one-step access to *N*-alkylated and *N*-arylated oxathiazinane heterocycles without the formation of competing aziridination side products. It should also be noted that while unsubstituted oxathiazinane heterocycles can be easily alkylated, we know of only example of oxathiazinane *N*-arylation.[63]

A variety of alkenyl sulfamates were prepared and tested with our optimized reaction protocol of catalytic $Pd_2(dba)_3$ and stoichiometric $Cu(OAc)_2$ heated in CH_3CN under 1 atm of O_2 (Table 3). 6-membered rings reliably formed with synthetically useful yields (56% to >90%). The diastereoselectivity of the reaction was found to be highly substrate dependent and ranged from reasonable (4:1, Table 3, **Entry 3**) to excellent (>20:1, Table 3, **Entry 4**). Seven membered ring formation was also possible, albeit in significantly lower yield (Table 3, **Entry 8**). Both *cis* and *trans* disubstituted alkenes engaged effectively. Overall, our reaction protocol was found to be compatible with a range of functional groups, including ethyl esters, morpholine amides, benzyl ethers, fluorinated arenes, and 1,3-benzodioxoles.

Under our optimized protocol, even when the scale was increased 20–45 times, the reactions continued to proceed with synthetically useful efficiency (Scheme 2). At a scale of 1.30 g (4.58 mmol, ~20-fold increase), (E)-hex-3-en-1-yl (4-methoxyphenyl)sulfamate cyclized with comparable yield to the reaction at 0.2 mmol (Scheme 2a). On smaller scale, a 10:1 mixture of trans/cis products formed; on larger scale, a 6:1 mixture of trans and cis products was isolated (Scheme 2a). At a scale of 1.74 g (9.09 mmol, ~45-fold increase), (E)-hex-3-en-1-yl methylsulfamate cyclized with a yield of 56% (Scheme 2b).

The resulting unsaturated [1,2,3]-oxathiazinane-2,2-dioxide heterocycles are versatile synthetic intermediates for a variety of transformations (Scheme 3). Hydrogenation to form a fully saturated [1,2,3]-oxathiazinane-2,2-dioxide with 10% Pd/C under 1 atm of H_2 proceeded in an excellent yield of 95% (Scheme 3a). Oxidation of the alkene with *m*CPBA to form the epoxide was also viable (Scheme 3b). The alkoxy-sulfonyl auxiliary was liberated *via* a smooth reaction with 2-naphthol (Scheme 3c).

In summary, we report the first examples of *aza*-Wacker cyclizations of sulfamate esters. The reactions are catalytic in $Pd_2(dba)_3$ and utilize $Cu(OAc)_2$ and O_2 as terminal oxidants. Our protocol is compatible with both *N*-alkyl and *N*-aryl sulfamates and tolerates a range of important functional groups. These reactions proceed in good yields on scales both large and small, and the resulting alkenyl oxathiazinane heterocycles are shown to be valuable synthetic intermediates. In time, we expect that this reaction will find use in both academic and industrial organic chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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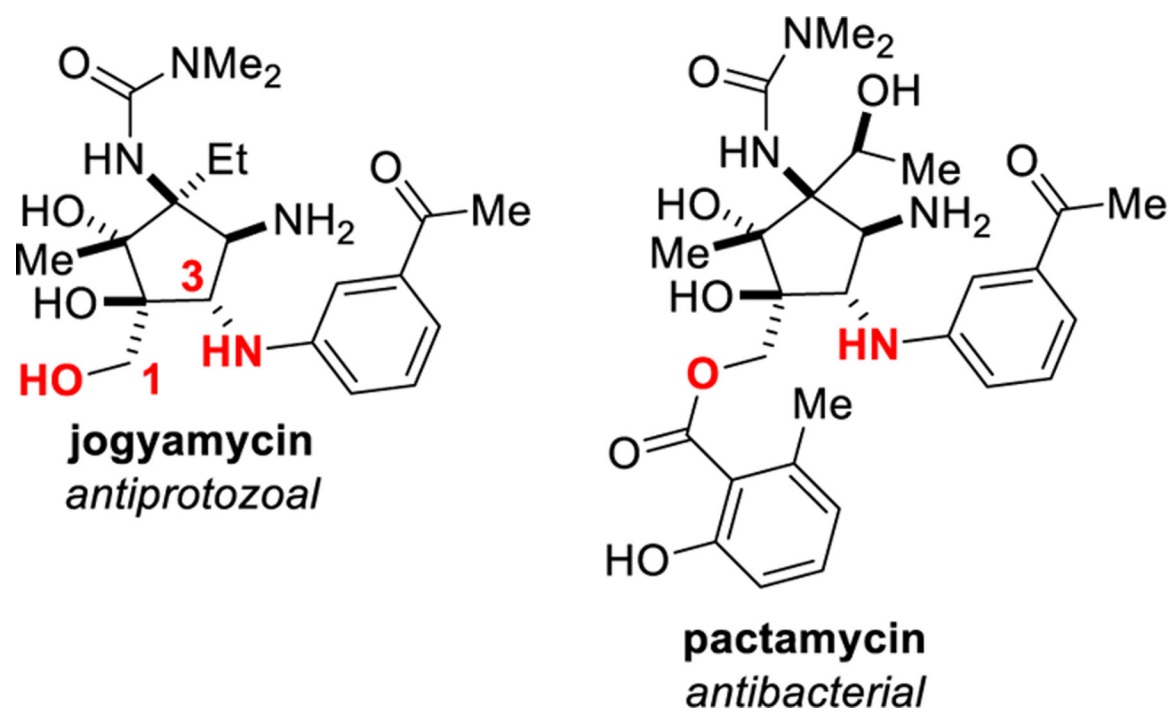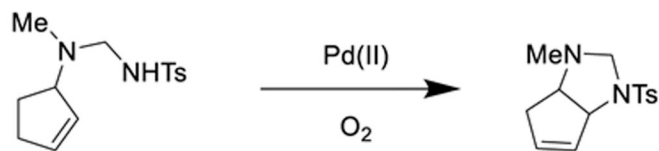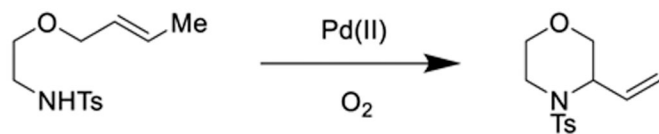
Figure 1.
1,3-amino alcohols are vital structural elements in biologically active molecules.
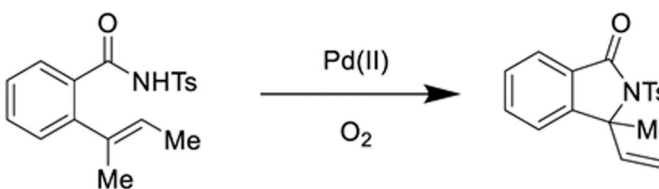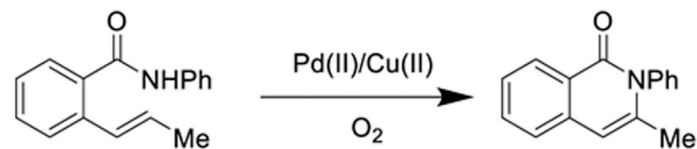
Hiemstra and co-workers

Stahl and co-workers

Stoltz and co-workers

Zhang and co-workers
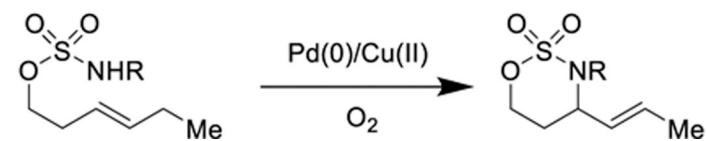
Sathyamoorthi and Shinde (this work)

Scheme 1.
Literature precedent inspires an *aza*-Wacker cyclinzation of sulfamate esters.

A)

1g *(1.30 gram scale)*

Pd/Cu
O$_2$ (1 atm)

MeCN
55 °C
78%

2g
6:1 trans: cis

B)

1a *(1.74 gram scale)*

Pd/Cu
O$_2$ (1 atm)

MeCN
55 °C
56%

2a
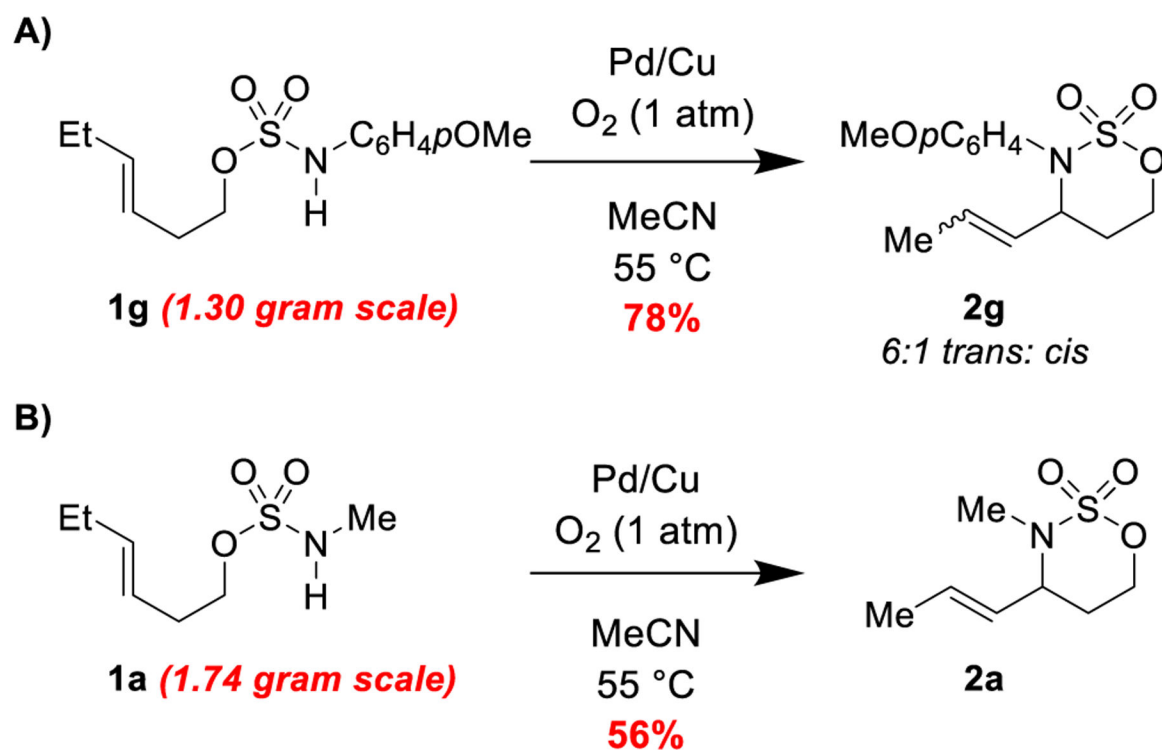
Scheme 2.
Oxdative cyclization scales successfully under standard conditions.

A)

B)

C)
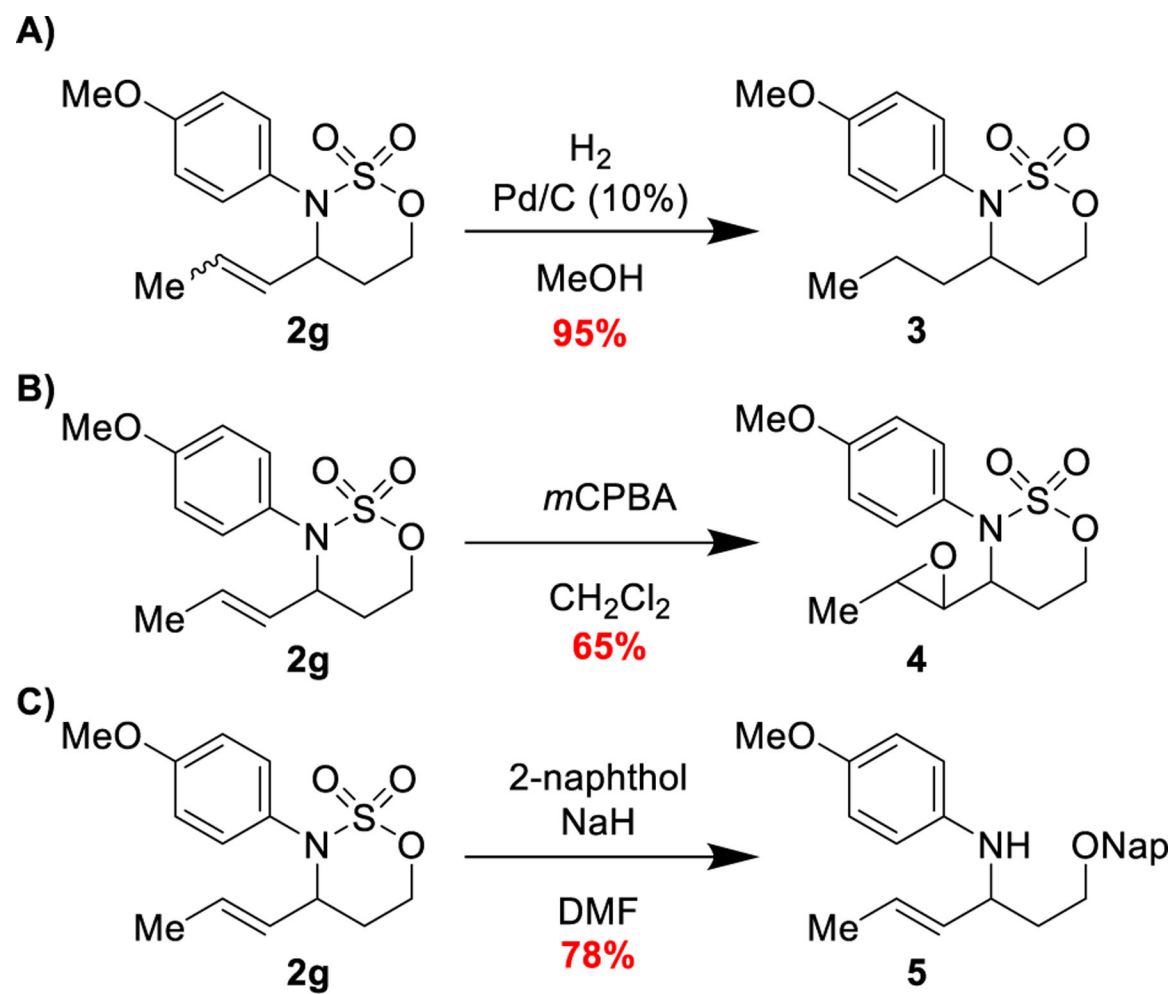
Scheme 3.
Alkenyl oxathiazinane heterocycles are versatile synthons.

Table 1.

Optimization of reaction conditions.

Entry	[Pd]	Solvent	Temp., Time	$2/1^b$
1^c	Pd(OAc)$_2$ (10%)	DMSO	55° C, 17 h	46:54
2	Pd(OAc)$_2$ (10%)	THF	55° C, 17 h	NR
3	Pd(OAc)$_2$ (10%)	Toluene	55° C, 17 h	NR
4^d	Pd(OAc)$_2$ (10%)	MeOH	55° C, 17 h	40:25
5	Pd(OAc)$_2$ (10%)	CH$_3$CN	55° C, 17 h	50:50
6	Pd(OAc)$_2$ (10%)	CH$_3$CN	55° C, 17 h	53:39
7	Pd(CH$_3$CN)$_2$(Cl)$_2$ (10%)	CH$_3$CN	55° C, 17 h	30:30
8	Pd(DPPF)Cl$_2$ (10%)	CH$_3$CN	55° C, 17 h	NR
9	Pd(TFA)$_2$ (10%)	CH$_3$CN	55° C, 17 h	50:30
10	Pd(OAc)$_2$ (10%)	CH$_3$CN	80° C, 17 h	56:28
11	Pd(OAc)$_2$ (10%)	CH$_3$CN	55° C, 26 h	56:30
12	White Catalyst^e	CH$_3$CN	55° C, 17 h	10:90
13	Pd$_2$(dba)$_3$ (10%)	CH$_3$CN	55° C, 17 h	62:07
14	Pd$_2$(dba)$_3$ (15%)	CH$_3$CN	55° C, 17 h	$70:00^f$

^{a}1 atm, unless mentioned otherwise

^{b}yields estimated by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene)

^{c}Without copper, conversion is ~30%; without O$_2$, a similar drop in yield is observed

^{d}O$_2$ pressure = 4 atm

^{e}1,2-Bis(phenylsulfinyl)ethane palladium (II) acetate (10 mol%)

^{f}At present, we are unable to account for the decreased mass balance

Table 2.

Structure-Reactivity relationship of sulfamate esters.

entry	substrate	product	yield (%)[a]
1	1a	2a	70
2	1b	2b	37[b]
3	1c	2c	15[b]
4	1d	—	NR
5	1e	2e	55[c]
6	1f	2f	74[d]
7	1g	2g	73[c]
8	1h-i	2h-i	R = OEt 80[c]
			R = morpholine 70[c]
9	1j	2j	45[b]

[a] isolated yield, unless otherwise mentioned

[b] yield estimated by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene)

[c] isolated as a 10:1 mixture of trans/cis isomers

[d] isolated as a 5:1 mixture of trans/cis isomers

TABLE 3.

Diverse alkenyl sulfamates engage productively.

entry	substrate	product	yield (%)[a]

1 — 1k-1l → 2k-2l — R = Me **68**; R = p-OMeC₆H₄ **93**

R = Me **68**

R = p-OMeC₆H₄ **93**

2 — 1m → 2a — **60**

3[b] — 1n → 2n — **83[c]**

4[d] — 1o → 2o — **67[e]**

5[f] — 1p-1r → 2p-r — Ar = Ph **94**; Ar = pFC₆H₅ **92**; Ar = **73**

6 — 1s-t → 2s-t — R = Me **65**; R = p-OMeC₆H₄ **70**

7 — 1u → 2u — **56[g]**

8 — 1v → 2v — **24**

[a] isolated yield, unless otherwise mentioned

[b] 1:1 mixture of cis/trans isomers

[c.]isolated as a 4:1 mixture of syn/anti diastereomers

[d.]1:1 mixture of cis/trans isomers

[e.]isolated as a single diastereomer

[f.]Ar = Ph, 4.6:1 mixture of trans/cis isomers; Ar = pFC$_6$H$_5$, 5.9:1 mixture of trans/cis isomers; Ar = 1,3-benzodioxole, 5:1 mixture of trans/cis isomers

[g.]isolated as a 1.6:1 mixture of trans/cis isomers