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Enantioselective Aza-Heck Cyclizations of *N*-(Tosyloxy)carbamates: Synthesis of Pyrrolidines and Piperidines

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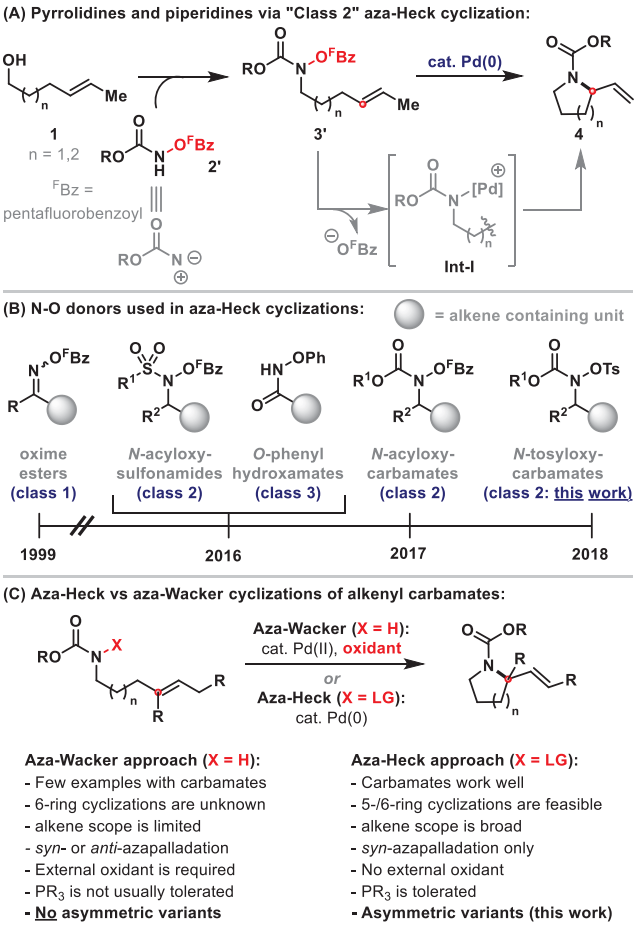
Supporting Information

ABSTRACT: Pd(0)-systems modified with SPINOL-derived phosphoramidate ligands promote highly enantioselective aza-Heck cyclizations of alkenyl *N*-(tosyloxy)-carbamates. The method provides versatile access to challenging N-heterocycles and represents the broadest scope enantioselective aza-Heck protocol developed to date.

There is a pressing demand for methods that provide modular and stereocontrolled access to chiral N-heterocyclic systems.[1] To address this, we described recently two-step protocols for the synthesis of pyrrolidines and piperidines (**4**) that exploit bifunctional amino reagents **2′** (Scheme 1A).[2,3] Here, Mitsunobu alkylation of **2′** with alkenyl alcohols **1** precedes Pd(0)-catalyzed aza-Heck cyclization to the target **4** (Scheme 1A). In this latter step, N−O oxidative addition[4] is followed by aza-palladation of the alkene,[5] a process that requires access to cationic intermediate **Int-I**.[2] "Class 1" aza-Heck cyclizations were pioneered by Narasaka and use pentafluorobenzoyl oxime esters as the N−O donor (Scheme 1B).[6−8] The "Class 2" processes shown in Scheme 1A,[2] in combination with Watson's "Class 3" methods,[9] expand the range of N−O donors available for aza-Heck chemistry. Importantly, these newer processes offer significantly broader scope than complementary aza-Wacker cyclizations of NH-nucleophiles, while at the same time circumventing the use of an external oxidant; a method comparison for carbamate-based processes is shown in Scheme 1C.[6,10a,b,e,g,h,j]

In principle, the aza-Heck approach is much better suited to enantioselective cyclizations than aza-Wacker processes.[10,11] This is because (a) oxidatively sensitive and highly tunable chiral P-ligands can be used and (b) alkene aza-palladation occurs exclusively via a *syn*-addition pathway (Scheme 1C).[2,6−9] However, these benefits are offset by the prescriptive ligand requirements of the aza-Heck processes developed so far. Indeed, only recently have efficient chiral ligands been developed for certain subsets of Class 1 processes,[8] and enantioselective Class 2 and 3 cyclizations have not been achieved. Herein, we address this issue by outlining highly efficient enantioselective 5- and 6-*exo* Class 2 cyclizations. The new method provides a range of challenging ring systems, including α-tetrasubstituted variants, with high levels of enantiocontrol. Two key advances underpin the work described here: (1) the first examples of the use of *N*-(tosyloxy)carbamates as N−O donors in aza-Heck cyclizations

Scheme 1. Introduction



and (2) the identification of SPINOL-derived phosphoramidates as effective ligand systems.[12] The resulting processes offer the most general enantioselective aza-Heck protocol developed to date[6,8] and, as such, provide an important contribution to this emerging and topical field.

Our studies commenced by evaluating a range of chiral ligands for the enantioselective cyclization of O^{F}Bz system **3a′**. As outlined in Table 1 chelating P,N- and P,P-systems **L1** and **L2** were not effective and afforded only traces of target **4a** (entries 1−2). Conversely, the use of monodentate phosphor-

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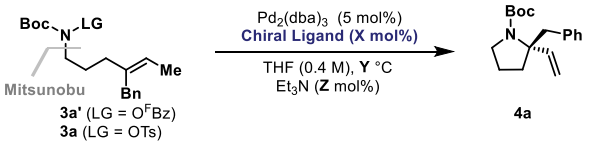
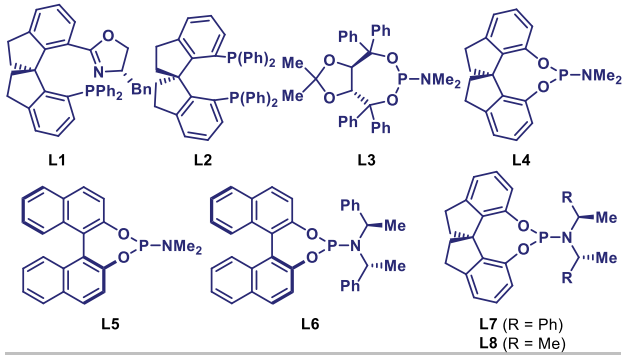
Table 1. Optimization of a 5-*exo* Aza-Heck Cyclization

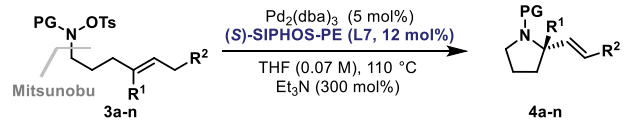


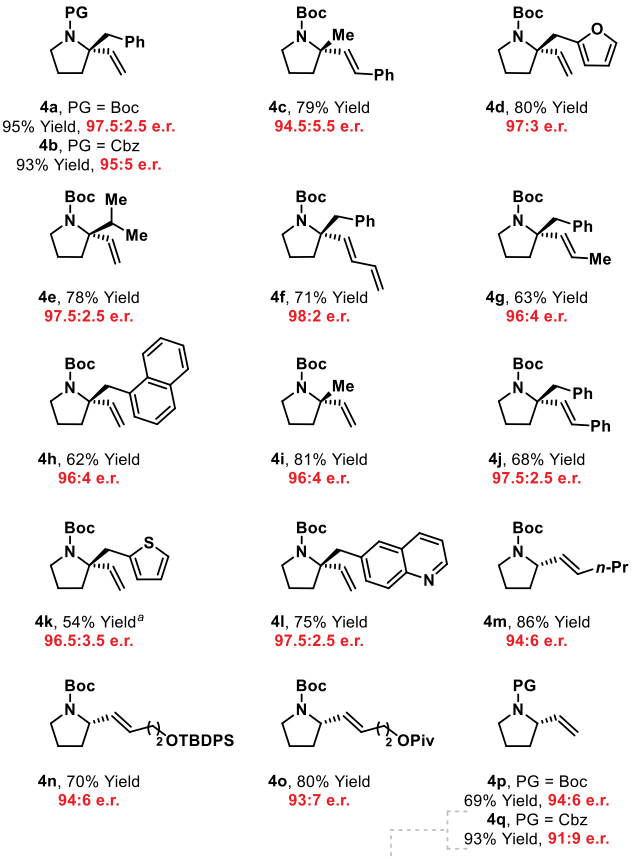
Entry	Ligand (X)	Y	Z	LG	Yield[a]	e.r.[b]
1	**L1** (20%)	130	100	O^FBz	trace	n.d.
2	**L2** (10%)	130	100	O^FBz	trace	n.d.
3	**L3** (20%)	130	100	O^FBz	62%	50:50
4	**L4** (20%)	130	100	O^FBz	65%	55:45
5	**L5** (20%)	130	100	O^FBz	59%	39:61
6	**L6** (20%)	130	100	O^FBz	60%	39:61
7	**L7** (20%)	130	100	O^FBz	74%	80:5:19.5
8	**L7** (20%)	130	100	OTs	75%	96.5:3.5
9	**L7** (12%)	130	100	OTs	72%	96:4
10[c]	**L7** (12%)	110	300	OTs	95%	97.5:2.5



[a]Isolated yield. [b]Determined by chiral SFC analysis. [c]A concentration of 0.07 M was used; n.d. = not determined.

Table 2. Enantioselective 5-*exo* Aza-Heck Cyclizations





Effects of varying the leaving group of **3q** (-OSO_2**R**) on the formation of **4q**:

R of -OSO_2**R** =	Me- (**3qa**)	*p*-$MeOC_6H_4$- (**3qb**)	*p*-FC_6H_4- (**3qc**)	*p*-$NO_2C_6H_4$- (**3qd**)
Yield and e.r. of **4q**	78% Yield 90:10 e.r.	85% Yield 91:9 e.r	76% Yield 92.5:7.5 e.r.	93% Yield 94:6 e.r.

[a]Run at 0.2 M.

amidate systems was more promising, such that **L3**–**L7** promoted chemically efficient cyclizations (entries 3–7). Of these, **L7** was most effective and provided **4a** in 74% yield and 80.5:19.5 e.r. (entry 7). At this stage, the influence of the leaving group (LG) was explored leading to the observation that OTs analogue **3a** cyclizes with higher levels of enantioselectivity to form **4a** in 96.5:3.5 e.r. (entry 8). Further optimization was achieved by variation of reaction temperature, concentration, and Et_3N loading. Ultimately, this led to the conditions outlined in entry 10 which deliver **4a** in 95% yield and 97.5:2.5 e.r. The efficient use of OTs activated system **3a** is significant because the tosylate unit is cheaper, less mass intensive, and easier to install than the pentafluorobenzoate leaving group used in previous work.[2,6–8]

The scope of the process for the construction of pyrrolidines is outlined in Table 2. Both N-Boc and N-Cbz protected systems can be used, with the latter offering marginally lower enantioselectivities; for example, cyclization of **3b** provided **4b** in 95:5 e.r. vs 97.5:2.5 e.r. for **3a** to **4a**. Note that **3a** and **3b** were readily prepared by Mitsunobu alkylation of BocNHOTs (**2a**) and CbzNHOTs (**2b**), respectively (see the Supporting Information (SI)). Using N-Boc protected systems **3c**–**l**, we have found that high levels of enantioinduction are maintained for cyclizations involving a range of sterically diverse trisubstituted alkenes.[13] Even system **3e**, which has a bulky isopropyl substituent at R^1, cyclized efficiently to provide **4e** in 97.5:2.5 e.r. The generality of the method for the construction of pyrrolidines bearing tetrasubstituted α-stereocenters is significant; prior methodologies for accessing ring systems of this type do not offer the same level of scope and versatility.[14]

The protocol also extends to 1,2-disubstituted alkenes, such that cyclization of N-Boc protected substrates **3m**–**p** generated **4m**–**p** in good to excellent yield and high enantioselectivity. Conversely, cyclization of N-Cbz system **3q** provided **4q** in only 91:9 e.r. To improve the enantioselectivity of this process we evaluated replacement of the tosylate leaving group of **3q** with other variants. These studies revealed that more electron-poor aryl sulfonates improve reaction efficiency, such that *p*-nitro system **3qd** generated **4q** in 93% yield and 94:6 e.r.[15] Accordingly, where required, fine-tuning of enantioselectivity can be achieved by variation of the leaving group (vide infra). Absolute stereochemical assignments of the products in Table 2 were made by comparison of specific rotation values of **4p** and **4q** to literature data and by single crystal X-ray diffraction analysis of the *p*-bromophenylsulfonamide derivative of **4a** (see the SI).

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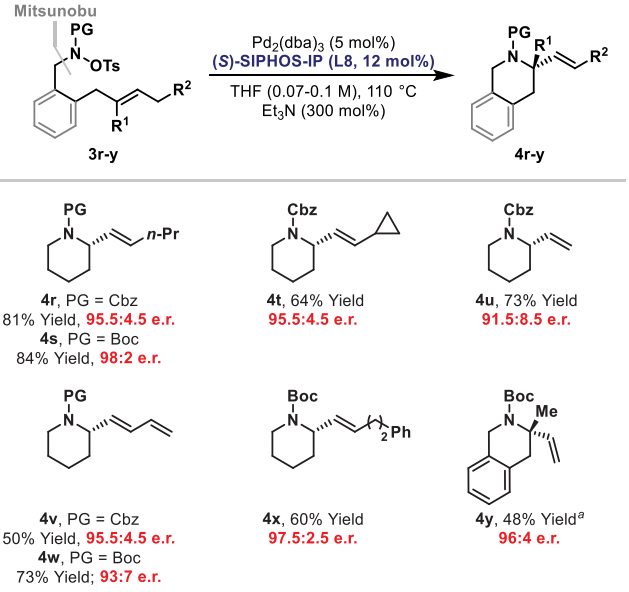
Extension of the enantioselective aza-Heck protocol to the provision of piperidines via 6-*exo* cyclization proved to be challenging. Exposure of **3r** to the conditions outlined in Table 1, entry 10 provided **4r** in 94.5:5.5 e.r., but in only 55% yield. Extensive efforts to improve reaction efficiency by variation of solvent, concentration, or base were not fruitful (see the SI). Ultimately, we found that this more demanding cyclization could be achieved efficiently by replacement of **L7** with the less sterically demanding ligand (*S*)-SIPHOS-IP (**L8**; see Table 1). Under these conditions, cyclization of **3r** provided **4r** in 81% yield and 95.5:4.5 e.r. (Table 3). N-Boc system **3s** also

Table 3. Enantioselective 6-*exo* Aza-Heck Cyclizations

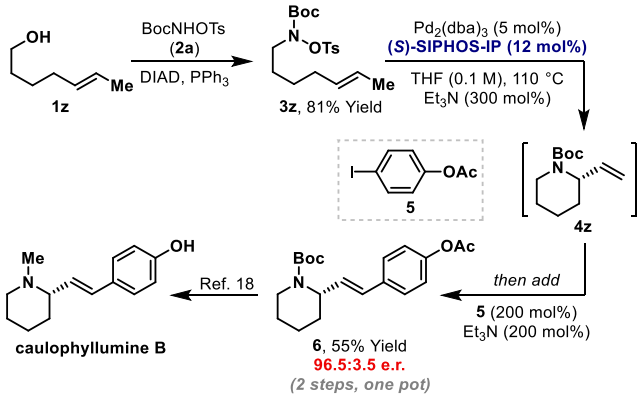


[a]Et_3N (500 mol %) was added, and **L7** was used in place of **L8**.

participated smoothly to generate **4s** in 98:2 e.r. and 84% yield. The protocol appears to be general for cyclizations involving *trans*-1,2-disubstituted alkenes such that **4t–x** were all formed with acceptable levels of efficiency.[16] Interestingly, **L8** is not especially effective for 5-*exo* cyclizations; for example, exposure of **3a** to the (*S*)-SIPHOS-IP system (**L8**) provided **4a** in only 34% yield (vs 95% yield with **L7**). At the current level of development, 6-*exo* cyclizations involving trisubstituted alkenes are demanding. We have to date been unable to devise acceptable conditions for conformationally flexible systems; however, processes of this type can be realized for the construction of challenging tetrahydroisoquinolines such as **4y**, which was accessed in 48% yield and 96:4 e.r. using **L7**. Here, the use of **L8** provided low levels of efficiency.

A key feature of the processes described here is that they are redox neutral. This contrasts with related Wacker-type processes, where the requirement for an external oxidant limits the potential for using highly tunable (but oxidatively sensitive) P-ligands to induce asymmetry.[10,11] Further, as noted in our earlier studies, nonenantioselective processes of this type do not offer high levels of scope for carbamate-based processes, especially with respect to ring size and alkene substitution.[2b,10e,g,h,j] A further benefit of operating in a redox neutral manifold is that the catalytic cycle is closed by release of a Pd(0)-catalyst and this offers opportunities for the design of powerful tandem processes. To demonstrate this, we prepared **3z** in 81% yield by Mitsunobu alkylation of bifunctional amino-reagent **2a** with (*E*)-hept-5-en-1-ol **1z** (Scheme 2). Note that the N–O bond of **2a** facilitates the

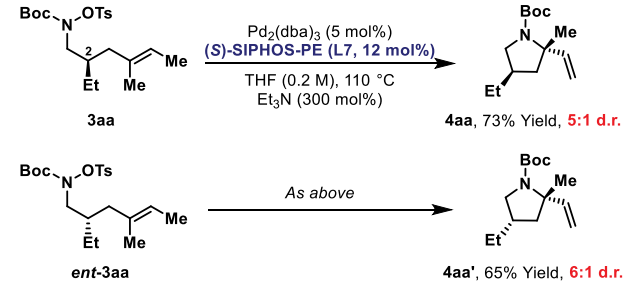
Scheme 2. Caulophyllumine B via a Tandem Aza-Heck/Heck Strategy



Mitsunobu reaction.[17] Enantioselective cyclization of **3z** under optimized aza-Heck conditions provided piperidine **4z**. This product was not isolated, and instead the Pd(0)-catalyst was harnessed for a subsequent Heck reaction, wherein addition of aryl iodide **5** effected C–H arylation to provide **6** in 96.5:3.5 e.r. and 55% yield for the one-pot two-step process. Conversion of **6** to the natural product caulophyllumine B has been achieved previously in one step.[18] The absolute stereochemical assignment of **6** was made by comparison of its specific rotation value to literature data. Similar analyses for **4u** and **4z** support the stereochemical assignments in Table 3.[19]

We have also evaluated the protocols described here in the diastereodivergent assembly of more heavily substituted pyrrolidines (Scheme 3). Exposure of stereodefined **3aa**

Scheme 3. Diastereoselective Cyclizations under Catalyst Control



(>98:2 e.r.), which is substituted at C-2, to optimized aza-Heck conditions using **L7** as ligand provided **4aa** in 73% yield and 5:1 d.r. Conversely, use of the same conditions for the cyclization of ***ent*-3aa** generated diastereomeric product **4aa′** in 6:1 d.r. Thus, the chiral Pd-catalyst can be used to enforce diastereocontrol during the assembly of these challenging pyrrolidine systems.[20] Further investigations into the scope of this approach are ongoing.

The mechanistic detail of the alkene aza-palladation step (cf. **Int-I** to **4**, Scheme 1A) that underpins the processes outlined here merits comment. Our collective studies indicate that alkene aza-palladation proceeds via a cationic pathway (e.g., via **Int-I**) for previous Class 1 and 2 processes that use

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pentafluorobenzoate as the leaving group.[2,7f] In these processes the equivalent of acid generated via the β-hydride elimination step triggers protodecarboxylation of the pentafluorobenzoate leaving group, thereby maintaining access to a cationic cycle.[7f] Cationic Heck-like manifolds accommodate bidentate chiral ligands, and this renders them ideal for enantioselective reaction development.[21] By contrast, optimal efficiencies are achieved in the current processes with only a 1:1.2 ratio of Pd/PR_3 (see Table 1). This observation is consistent with cyclization occurring via a neutral pathway, where the sulfonate leaving group is ligated to the Pd-center during alkene aza-palladation.[22] In this scenario, the increased enantioselectivity observed in the cyclizations of **3qd** vs **3q** can be attributed to an electronic effect (see Table 2). This interpretation must be treated with caution, and alternative rationalizations cannot be discounted on the basis of available data.

In summary, we show that Pd(0)-systems modified with SPINOL-derived phosphoramidate ligands promote highly enantioselective 5- and 6-*exo* aza-Heck cyclizations of alkenyl *N*-(tosyloxy)carbamates. The substrates are easily accessed by Mitsunobu alkylation of bifunctional amino reagent BocNHOTs (**2a**) or CbzNHOTs (**2b**), and this underpins a direct route to enantioenriched pyrrolidines and piperidines that are challenging or inaccessible using conventional approaches. In particular, this new aza-Heck method is complementary to related oxidative aza-Wacker cyclizations (see Scheme 1C); highly enantioselective variants of the latter are rare and, to our knowledge, have not been achieved for carbamate-based nucleophiles.[10,11] Ultimately, the aza-Heck method described here is able to provide high enantioselectivity because external oxidants are avoided, and this allows the use of highly tunable chiral P-based ligands. These considerations are one of several key benefits of the aza-Heck approach,[6a] and the continued development of this manifold is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12689.

Experimental details and characterization data (PDF)

Crystallographic data for a derivative of **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) The geometry of the alkene is an important factor in determining the enantioselectivity of the product. For example, the (*Z*)-isomer of **3q** provided **4q** in only 76% yield and 75:25 e.r. under the conditions shown in Table 2 (see the SI). At the present level of development, 5-*exo* cyclizations involving tetrasubstituted alkenes are not efficient; a representative example is given in the SI.

(14) Highly enantioselective catalytic approaches to α-tetrasubstituted pyrrolidines are rare. Selected examples: (a) Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.-G.; Maruoka, K. Catalytic Asymmetric Synthesis of Cyclic α-Alkyl-Amino Acid Derivatives by C,N-Double Alkylation. *Tetrahedron* **2010**, *66*, 4900. (b) Farid, U.; Wirth, T. Highly Stereoselective Metal Free Oxyaminations Using Chiral Hypervalent Iodine Reagents. *Angew. Chem., Int. Ed.* **2012**, *51*, 3462. (c) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. Copper Catalyzed Enantioselective Intramolecular Aminooxygenation of Alkenes. *J. Am. Chem. Soc.* **2008**, *130*, 17638. (d) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. Enantioselective Bromoaminocyclization Using Amino−Thiocarbamate Catalysts. *J. Am. Chem. Soc.* **2011**, *133*, 9164.

(15) A range of other sterically and electronically distinct leaving groups were evaluated (see the SI).

(16) The alternate *cis*-alkene isomer of **4s** cyclized in 18% yield and 96:4 e.r. under the conditions shown in Table 3 (see the SI).

(17) NH-carbamates required for aza-Wacker cyclizations (cf. Scheme 1C) cannot usually be prepared *directly* by Mitsunobu reaction: Bittner, S.; Assaf, Y.; Krief, P.; Pomerantz, M.; Ziemnicka, B. T.; Smith, C. G. Synthesis of *N*-Acyl-, *N*-Sulfonyl-, and *N*-Phosphinylphospha (λ^5)-azenes by a Redox-Condensation Reaction Using Amides, Triphenylphosphine, and Diethyl Azodicarboxylate. *J. Org. Chem.* **1985**, *50*, 1712.

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(19) **4z** could be isolated in 76% yield and 96.5:3.5 e.r. (see the SI).

(20) Under our previously reported nonenantioselective conditions (see ref 2a) cyclization of ***ent*-3aa** gives **4aa′** in 36% yield and 2:1 d.r.

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(22) Enantioselective "neutral" Heck reactions are rare (see ref 21).

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