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Asymmetric NHC-Catalyzed Redox α-Amination of α-Aroyloxyaldehydes

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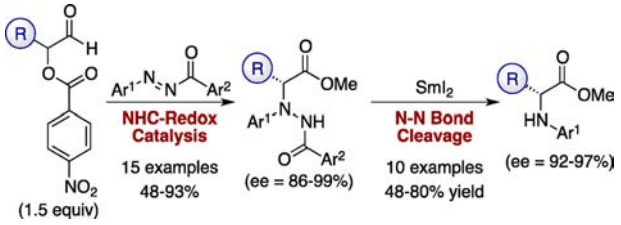
ABSTRACT



Asymmetric α-amination through an N-heterocyclic carbene (NHC)-catalyzed redox reaction of α-aroyloxyaldehydes with *N*-aryl-*N*-aroyldiazenes to form α-hydrazino esters with high enantioselectivity (up to 99% ee) is reported. The hydrazide products are readily converted into enantioenriched *N*-aryl amino esters through samarium(II) iodide mediated N−N bond cleavage.

The enantioselective organocatalytic α-amination of carbonyl compounds using a variety of electrophilic nitrogen sources has received much attention due to the prevalence of the resulting α-amino carbonyl motif within biologically active compounds.[1] For example, a common strategy involves addition to azodicarboxylates using either enamine or hydrogen-bonding organocatalysts.[2,3]

N-Heterocyclic carbene (NHC)-redox catalysis, promoted through addition of an NHC to an aldehyde bearing an α-reducible functional group, allows access to a range of catalytic intermediates including acyl azoliums, azolium enolates, and homoenolates.[4] Despite the widely demonstrated utility of NHC-redox catalysis, there are only limited reports of its use in amination processes. For example, Scheidt et al. first demonstrated that enals undergo NHC-catalyzed redox *β*-amination *via* a homoenolate intermediate with *N*-aryl-*N*-aroyldiazenes, followed by cyclization, to form (±)-pyrazolidinones (Scheme 1a).[5] Ye et al. subsequently found that azolium enolate intermediates accessed through direct addition of an NHC to disubstituted ketenes undergo [4 + 2]-cycloadditions with *N*-aryl-*N*-aroyldiazenes to form 1,3,4-oxadiazin-6-ones (Scheme 1b).[6]

Herein we report an asymmetric NHC-catalyzed redox α-amination using α-aroyloxyaldehydes as azolium enolate precursors. Reaction with *N*-aryl-*N*-aroyldiazenes forms α-hydrazino esters with excellent enantioselectivity (Scheme 1c).[7] Further derivatization of these α-hydrazino esters into the corresponding *N*-aryl amino esters through

(1) For selected reviews, see: (a) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917–958. (b) Baktharaman, S.; Hili, R.; Yudin, A. K. *Aldrichimica Acta* **2008**, *41*, 109–119. (c) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671. (d) Guillena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. (f) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292–4300. (g) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377–1385. (h) Erdik, E. *Tetrahedron* **2004**, *60*, 8747–8782. (i) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

(2) For selected examples, see: (a) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657. (c) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121. (d) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044–16045.

(3) Recently MacMillan et al. reported an elegant direct α-amination of aldehydes using photoredox catalysis; see: Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521–11524.

(4) For reviews on NHC-redox catalysis, see: (a) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906–4917. (b) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617–1639. (c) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295–2309. (d) Rong, Z. Q.; Zhang, W.; Yang, G. Q.; You, S. L. *Curr. Org. Chem.* **2011**, *15*, 3077–3090.

(5) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740–2741.

(6) Huang, X. L.; He, L.; Shao, P. L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192–195.

(7) For our complementary isothiourea catalyzed synthesis of α-aryl α-hydrazino esters, see: Morrill, L. C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci.* **2012**, *3*, 2088–2093.

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Scheme 1. NHC-Catalyzed Amination Reactions

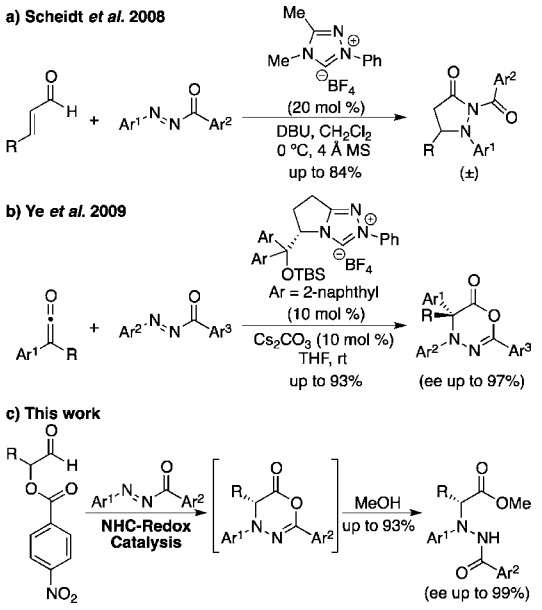
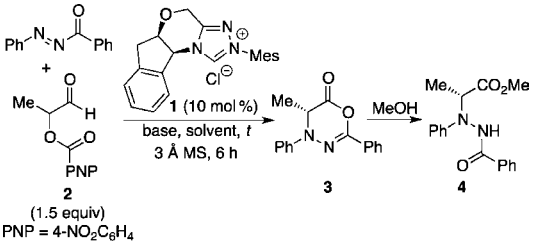


Table 1. Optimization



entry	base	solvent	*t* (°C)	prod.	conversion (%)[a]	ee (%)[b]
1	Cs_2CO_3	THF	rt	NA	0	NA
2	K_2CO_3	THF	rt	**3**	70	90
3	Et_3N	THF	rt	**3**	93	90
4	Et_3N	CH_2Cl_2	rt	**3**	>99	92
5	Et_3N	CH_2Cl_2	0	**3**	>99 (65[c])	95
6[d]	Et_3N	CH_2Cl_2	0	**4**	>99 (89[c])	96

[a] Conversion into product determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by HPLC analysis. [c] Isolated yield. [d] Reaction quenched with MeOH.

samarium(II) iodide mediated N−N bond cleavage has also been investigated.

As we have previously demonstrated, α-aroyloxyaldehydes are bench stable precursors for the NHC-catalyzed generation of both acyl azolium and azolium enolate intermediates.[8] They are readily prepared on gram scale from the parent aldehyde and 4-nitrobenzoic acid using Ishihara et al.'s α-oxyacylation methodology[9] and can be stored for a number of months without decomposition. We envisaged that azolium enolate intermediates generated through addition of an NHC to α-aroyloxyaldehydes would undergo [4 + 2] cycloadditions with *N*-aryl-*N*-aroyldiazenes to form 1,3,4-oxadiazin-6-ones, which could then be ring opened with methanol to form α-hydrazino esters.[10−12]

First the reaction between α-aroyloxyaldehyde **2** and *N*-phenyl-*N*-benzoyldiazene using 10 mol % NHC pre-catalyst **1** was investigated.[13] Initial studies found that using triethylamine as a base was more effective than inorganic bases such as cesium or potassium carbonate, leading to 93% conversion into cycloadduct **3** in 90% ee after 6 h (Table 1, entries 1−3).[14,15] Switching the solvent to dichloromethane resulted in complete conversion into **3** (Table 1, entry 4), while starting the reaction at 0 °C improved the ee to 95% without reducing the conversion (Table 1, entry 5). However, despite high conversion into product the isolated yield of 1,3,4-oxadiazin-6-one **3** was only 65% due to the instability of the heterocycle to chromatographic purification on silica.[16] This problem was readily overcome by ring-opening product **3** *in situ* with methanol, allowing α-hydrazino ester **4** to be isolated in 89% yield and 96% ee (Table 1, entry 6).

With an optimized protocol in hand, the scope of the reaction was investigated using a series of *N*-aryl-*N*-aroyldiazenes (Table 2). The reaction of α-aroyloxyaldehyde **2** with electron-rich *N*-aryl substituted diazenes (4-$MeOC_6H_4$ and 3,4-$(MeO)_2C_6H_3$) required an electron-withdrawing *N*-aroyl component (4-$CF_3C_6H_4$) to maintain high yields, with α-hydrazino esters **5** and **6** isolated in 69% and 93% yield, respectively. In contrast, electron-deficient *N*-aryl substituted diazenes (4-$CF_3C_6H_4$ and 4-NCC_6H_4) formed α-hydrazino esters **7** and **8** in reduced yields (56% and 48% respectively) presumably due to competitive side reactions

(8) (a) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373–375. (b) Davies, A. T.; Taylor, J. E.; Douglas, J.; Collett, C. J.; Morrill, L. C.; Fallan, C.; Slawin, A. M. Z.; Churchill, G.; Smith, A. D. *J. Org. Chem.* **2013**, *78*, 9243–9257.

(9) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331–5334.

(10) For examples of α-haloaldehydes as azolium enolate precursors in NHC-catalyzed redox [4 + 2] cycloadditions, see: (a) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089. (b) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817–3820. (c) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 3934–3937. (d) Yang, L. M.; Wang, F.; Chua, P. J.; Lv, Y. B.; Zhong, L. J.; Zhong, G. F. *Org. Lett.* **2012**, *14*, 2894–2897. (e) Jian, T.-Y.; Sun, L.-H.; Ye, S. *Chem. Commun.* **2012**, *48*, 10907–10909.

(11) Chi et al. have shown that azolium enolates can be accessed through NHC addition to 4-nitrophenyl esters followed by deprotonation; see: (a) Hao, L.; Du, Y.; Lv, H.; Chen, X. K.; Jiang, H. S.; Shao, Y. L.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154–2157. (b) Hao, L.; Chuen, C. W.; Ganguly, R.; Chi, Y. R. *Synlett* **2013**, *24*, 1197–1200. (c) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956–4959.

(12) Azolium enolates can also be accessed from unsubstituted aldehydes under oxidative conditions; see: (a) Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 12330–12333. (b) Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 50–53.

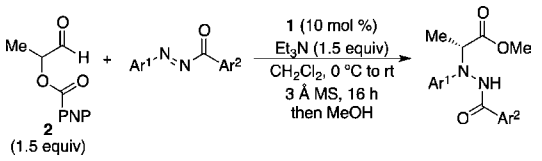
(13) We found diazodicarboxylates to be completely unreactive under a number of different conditions.

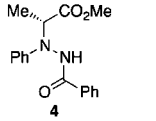
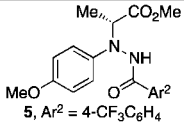
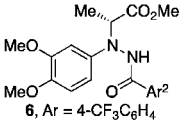
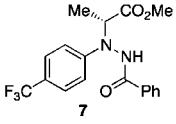
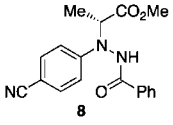
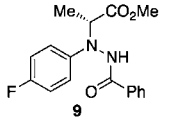
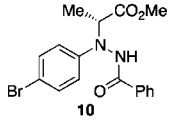
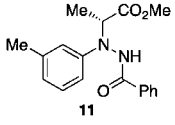
(14) Authentic racemic samples of all products were prepared using (*rac*)-**1** as the catalyst.

(15) Absolute configuration assigned by comparison of the specific rotation of cleaved *N*-aryl α-amino esters with the literature. (*R*)-**26** $[\alpha]_D^{20}$ −28.4 (*c* 1.48 in $CHCl_3$) {Lit. (*S*)-**26** $[\alpha]_D^{20}$ +26.6 (*c* 1.3 in $CHCl_3$)}. McKerrow, J. D.; Al-Rawi, J. M.; Brooks, P. *Asian J. Chem.* **2012**, *24*, 1227–1236.

(16) Upon isolation, heterocycle **3** is stable for up to *ca.* 1 month when stored in a freezer before undergoing ring opening.

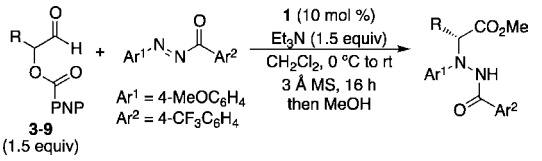
Table 2. Variation of the *N*-Aryl-*N*-aroyldiazene

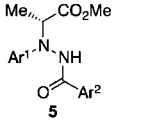
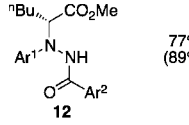
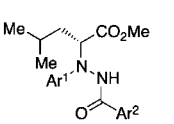
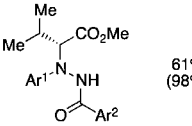
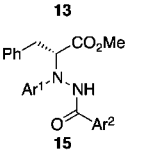
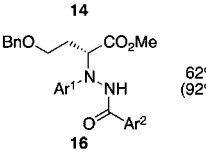
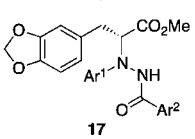
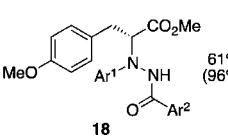


product	yield[a] (ee)[b]	product	yield[a] (ee)[b]
 **4**	89% (96%)	 **5**, Ar² = 4-CF₃C₆H₄	69% (92%)
 **6**, Ar = 4-CF₃C₆H₄	93% (86%)	 **7**	56% (99%)
 **8**	48% (96%)	 **9**	68% (94%)
 **10**	83% (97%)	 **11**	63% (94%)

[a] Isolated yields. [b] ee determined by HPLC analysis.

Table 3. Variation of the α-Aroyloxyaldehyde



product	yield[a] (ee)[b]	product	yield[a] (ee)[b]
 **5**	69% (92%)	 **12**	77% (89%)
 **13**	70% (93%)	 **14**	61% (98%)
 **15**	90% (98%)	 **16**	62% (92%)
 **17**	75% (96%)	 **18**	61% (96%)

[a] Isolated yields. [b] ee determined by HPLC analysis.

between the NHC and the diazene. This was most noticeable using an *N*-aryl 4-$NO_2C_6H_4$ substituted diazene, which underwent significant decomposition and gave low yields of the desired α-hydrazino ester even when the diazene was added to the reaction dropwise *via* syringe pump over a number of hours. Halogen substituents were well tolerated, with α-hydrazino esters **9** and **10** isolated in good yields and excellent ee. *N*-Aryl substitution in the *meta*-position was also tolerated, with *m*-tolyl hydrazide **11** isolated in 64% yield and 94% ee. However, *N*-aryl *ortho*-substitution was not possible, with an *o*-tolyl substituted diazene giving poor conversion into the corresponding hydrazide.

We next explored the scope of the α-aroyloxyaldehyde in the NHC-catalyzed redox α-amination with *N*-4-(methoxy)phenyl-*N*-4-(trifluoromethyl)benzoyl diazene under the standard reaction conditions (Table 3). Straight chain alkyl, *β*- and *γ*-branched alkyl, and benzyl substituted α-aroyloxyaldehydes were well tolerated, forming α-hydrazino esters **12**−**18** in good yield and excellent enantioselectivity (61−90% yield, 89−98% ee). The formation of α-hydrazino ester **14** is particularly notable, as *β*-branched substituents are notoriously poorly tolerated in reactions of azolium enolates.[11c,17] This methodology therefore allows simple aldehydes to be functionalized in two steps *via* the α-aroyloxyaldehyde into synthetically useful enantioenriched α-hydrazino esters.

The synthetic utility of the α-hydrazino ester products was demonstrated through samarium(II) iodide mediated N−N bond cleavage into the corresponding *N*-aryl amino esters.[18] The synthesis of *N*-aryl amino acid derivatives is of importance due to the presence of this motif within pharmacologically important molecules and is often achieved through transition-metal catalyzed *N*-arylation.[19] This methodology provides a simple, racemization-free alternative for the synthesis of novel *N*-aryl amino esters. For example, α-hydrazino ester **5** was readily cleaved through dropwise addition of freshly prepared SmI_2 (*ca.* 0.1 M in THF) at −78 °C in methanol to form *N*-aryl amino ester **19** in 70% yield and 92% ee.[20] The reaction proceeded cleanly, with

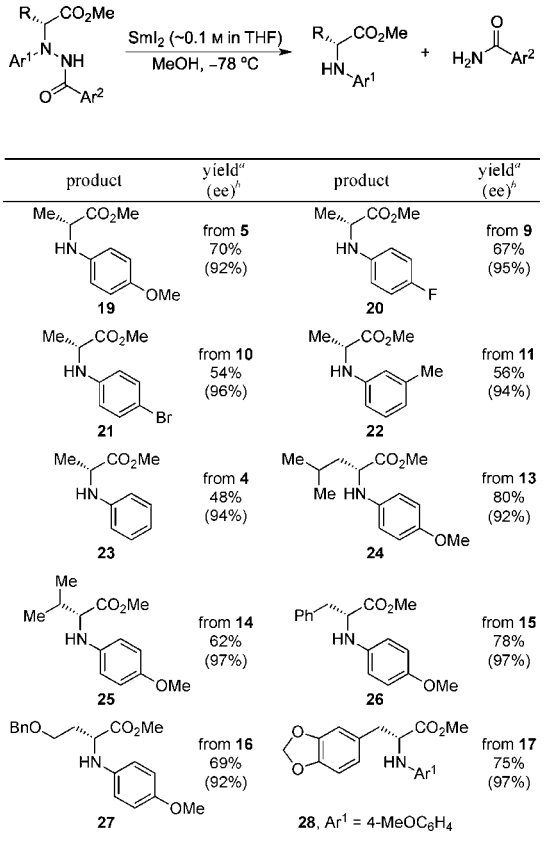
(17) Further increasing the steric demand of the α-aroyloxyaldehyde substituent to either α-^{t}Bu, or α,α-cyclopentyl (to give a quaternary center in the product) gave no reaction.

(18) For selected examples of SmI_2 mediated N−N bond cleavage of related substrates, see: (a) Theodorou, A.; Papadopoulos, G. N.; Kokotos, C. G. *Tetrahedron* **2013**, *69*, 5438–5443. (b) Liu, C.; Zhu, Q.; Huang, K.-W.; Lu, Y. *Org. Lett.* **2011**, *13*, 2638–2641. (c) Shigenaga, A.; Yamamoto, J.; Nishioka, N.; Otaka, A. *Tetrahedron* **2010**, *66*, 7367–7372. (d) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614–11615. (e) Chowdari, N. S.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 867–870.

(19) For selected examples of *N*-arylation of α-amino acid derivatives, see: (a) Hammoud, H.; Schmitt, M.; Blaise, E.; Bihel, F.; Bourguignon, J. J. *J. Org. Chem.* **2013**, *78*, 7930–7937. (b) Dong, J. Y.; Wang, Y.; Xiang, Q. J.; Lv, X. R.; Weng, W.; Zeng, Q. L. *Adv. Synth. Catal.* **2013**, *355*, 692–696. (c) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. (d) Ma, D.; Yao, J. *Tetrahedron: Asymmetry* **1996**, *7*, 3075–3078.

(20) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2012**, *77*, 3049–3059.

Table 4. Samarium(II) Iodide Mediated N−N Bond Cleavage

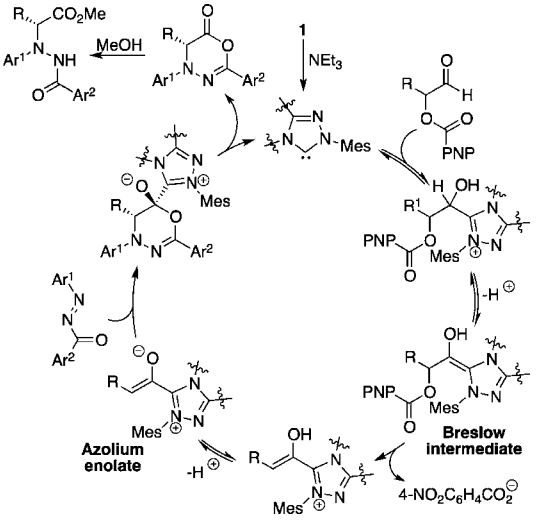


[a] Isolated yields. [b] ee determined by HPLC analysis.

the product obtained after straightforward chromatographic separation from the primary amide byproduct. The generality of this process was demonstrated through the N−N bond cleavage of a selection of α-hydrazino esters, giving a range of *N*-aryl amino esters **20**−**28** in good yield (48−80%) without any observed erosion in enantioselectivity (Table 4). The absolute (*R*)-configuration of the *N*-aryl amino esters was confirmed through *N*-PMP deprotection of **26** into phenylalanine methyl ester with ceric ammonium nitrate (CAN) and comparison of its specific rotation with the literature.[21]

The proposed catalytic cycle is shown in Scheme 2. Initially the free NHC, generated *in situ* through deprotonation of NHC precursor **1**, adds to the α-aroyloxyaldehyde to form an initial adduct.[22] Previously reported

Scheme 2. Proposed Catalytic Cycle



mechanistic studies through measurement of a kinetic isotope effect suggest that subsequent deprotonation of this adduct to form the Breslow intermediate is kinetically significant in NHC-catalyzed redox reactions of α-aroyloxyaldehydes.[8b] Elimination of *p*-nitrobenzoate, followed by deprotonation, forms the key azolium enolate intermediate. Computational studies by Bode et al. on the reaction of a related azolium enolate with a simple enone lead us to suggest that the azolium enolate and the diazene undergo an asynchronous *endo*-hetero-Diels−Alder reaction.[23] The catalyst can then be regenerated and release the 1,3,4-oxadiazin-6-one product that can either be isolated or ring opened with methanol.

In conclusion, we have developed an enantioselective NHC-catalyzed redox α-amination of α-aroyloxyaldehydes with *N*-aryl-*N*-aroyldiazenes to form a wide range of enantioenriched α-hydrazino esters. These synthetically useful hydrazide products are readily converted into *N*-aryl amino esters without loss in enantioselectivity through treatment with samarium(II) iodide.

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

The authors declare no competing financial interest.

(21) See Supporting Information for experimental details. Phenylalanine methyl ester from **26** $[\alpha]_D^{20}$ −31.3 (*c* 1.2 in EtOH) {Lit. (*R*)-phenylalanine methyl ester $[\alpha]_D^{23}$ −32.2 (*c* 1.0 in EtOH)}. Davies, S. G.; Garner, A. C.; Ouzman, J. V. A.; Roberts, P. M.; Smith, A. D.; Snow, E. J.; Thomson, J. E.; Tamayo, J. A.; Vickers, R. J. *Org. Biomol. Chem.* **2007**, *5*, 2138–2147.

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