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Auxiliary-Controlled Asymmetric [3+2]-Dipolar Cycloaddition of Azomethine Ylides Generated from Au-Catalyzed Intramolecular Redox Reaction of Nitronyl Alkynes

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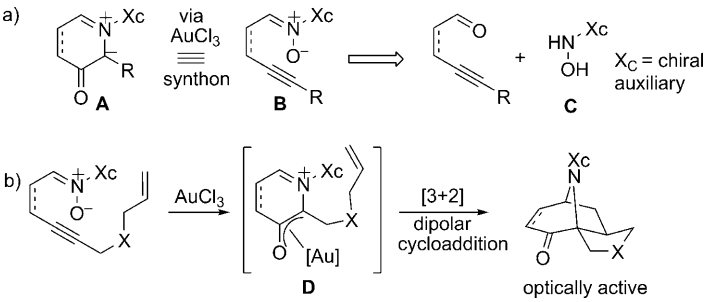
Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

1,3-Dipolar cycloaddition of azomethine ylides is one of the most-powerful approaches for the synthesis of pyrrolidine derivatives because it can create a large number of stereogenic centers in a single step.[1] Pyrrolidines occur widely in natural products and pharmaceuticals and, therefore, delivering these skeletons in their optically active forms represents a highly desirable goal.[2] Recently, we reported that gold-catalyzed redox reactions of nitronyl alkynes can generate an azomethine ylide for [3+2]-dipolar cycloaddition.[3] Such a N–O bond redox process can bypass the preparation of diazo-precursors that could entail an explosion hazard and/or atom-inefficiency and multiple bonds in the complex bicyclic skeleton are stereoselectively formed in an efficient manner from readily available precursors. Exploiting this synthetic equivalence between 3-oxidopyridinium betaines (**A**) and nitronyl alkynes (**B**, Scheme 1a),[4] the incorporation of chirally modified hydroxylamine derivatives (**C**) afforded the azabicyclo[3,2,1]octanes in an optically active form (Scheme 1b).[5–7] However, the precedent for chirally modified azomethine ylides with a removable auxiliary group is limited and often mediocre diastereoselectivities were reported.[5] Herein, we report that electronic tuning of



Scheme 1. Asymmetric dipolar cycloaddition using chiral hydroxylamine auxiliary by electronic tuning.

α-methylbenzylamine derivatives (X_c) as a removable auxiliary effectively controls the C–N rotamers and thus results in an excellent level of diastereofacial control in the intramolecular [3+2] cycloaddition of azomethine ylides generated in-situ from gold(III)-catalyzed redox reactions.

At the outset of our study, we decided to study the influence of the steric and electronic environments of azomethine ylides on the asymmetric dipolar cycloaddition. Despite significant efforts to modify chiral azomethine ylides, there has been limited success in improving facial selectivities, often requiring the introduction of additional chiral elements.[5c,d] Surprisingly, the effect of electronic tuning of *N*-α-methylbenzyl azomethine ylides has not been examined to our knowledge. Our initial study (Table 1) started with hydroxylamines (**1a–b**) derived from simple amino acids, which gave poor diastereoselectivities (Table 1, entries 1 and 2). On the other hand, cyclohexanone-derived hydroxylamines (**1c–e**) gave a satisfactory selectivity, but an attenuated reactivity presumably owing to the sterically hindered chiral environment (Table 1, entries 3–5) and presented further problems associated with their later detachment. We next turned to α-methylbenzyl hydroxylamine derivatives (**1f–I**; Table 1, entries 6–9). Chiral racemic **1f** gave mediocre facial selectivity (4.34:1) owing to free rotation around

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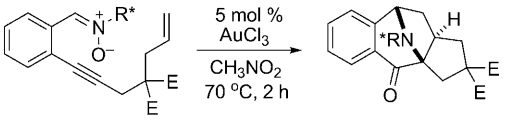
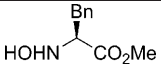
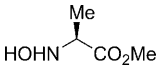
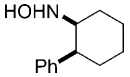
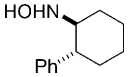
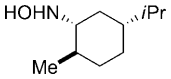
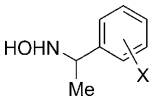
Table 1. Effect of hydroxylamine scaffolds on the diastereoselectivity.



2aa–2ai (E = CO_2Et) **3aa–3ai**

Entry[a]	R*NHOH		Yield[b]	d.r.[c]
1		**1a**	50	2.71:1
2		**1b**	78	2.34:1
3		**1c**	63	>20:1
4		**1d**	59	>20:1
5		**1e**	50	>20:1
6[d]		**1f** (X = H)	55	4.34:1
7[d]		**1g** (X = 4-OMe)	67	3.86:1
8[d]		**1h** (X = 4-Cl)	62	7.59:1
9[d]		**1i** (X = 4-NO_2)	78	>20:1

[a] Nitrone **2a-i** were prepared by condensation of the aldehyde precursor with the corresponding hydroxylamines. [b] Yield of isolated product after column chromatography on silica gel. [c] Diastereoselectivity was determined from the crude ^{1}H NMR spectra as well as HPLC analysis. [d] Racemic hydroxylamines **1** were used.

the C–N bond, in line with the intermolecular results by Padwa et al.[5a] To our delight, with *N*-(1-(*para*-nitrophenyl)ethyl) hydroxyl amine (**1i**), both satisfactory yield (78%) and a clean single diastereomer was observed in the crude ^{1}H NMR spectrum (d.r. > 20:1; Table 1, entry 9). Intriguingly, we noticed a trend that electron-deficient derivatives showed both higher selectivity and higher yield than those with electron-rich substituents. It is noteworthy that the C–N bond rotation (and thus the facial selectivity on azomethine ylides, see below, Figure 1) could be completely controlled simply by tuning of the electronic properties of the α-methylbenzyl group, without the need for a conformationally rigid cyclic azomethine ylide.[5e]

We next prepared **1i** in its optically active form (Scheme 2). Whilst the procedure for converting amines into their corresponding hydroxylamines reported by Fukuyama and co-workers could be applicable to the synthesis of optically active **1i**,[8] the optically pure α-methyl-*para*-nitrobenzylamine precursor for **1i** was rather expensive and thus we sought to resolve racemic hydroxylamines **1i** using diastereomeric salt formation. After some trials, we found that (*R*)-(−)-mandelic acid is an effective resolving agent for **1i**. After a single recrystallization from propan-2-ol, (*S*)-(+)-**1i**·MA (mandelate) was obtained in 47% *ee* from the crystal, along with 33% *ee* of (*R*)-(−)-**1i**·MA in the mother liquor. Iterative recrystallization of (*S*)-(+)-**1i**·MA (47% *ee*) twice increased the enantioselectivity to 95.4% *ee* (31% overall yield).[9] For (*R*)-(−)-**1i**·MA, anion exchange with tartrate was found to be more efficient, which similarly gave crystals of (*R*)-(−)-**1i**·TA (tartrate) with >95% *ee* after iterative recrystallizations (x5) from ethanol.

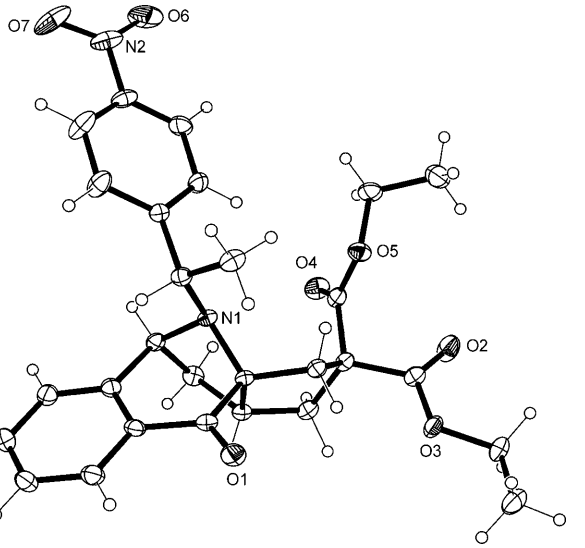
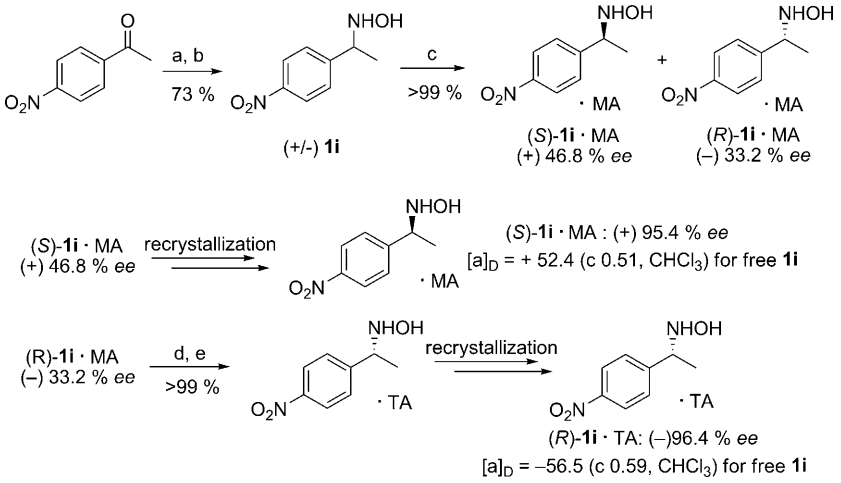


Figure 1. ORTEP of chiral **3ai** obtained from (*S*)-(+)-**1i**: Determination of absolute and relative stereochemistry.[9]

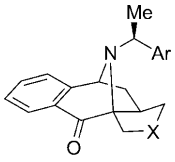
With either enantiomeric forms of **1i** in hand, we examined the scope of this chiral auxiliary in the gold-catalyzed redox-[3+2]-dipolar cycloaddition tandem reaction. Direct condensation of the (*S*)-(+)-**1i**·MA salt (95.4~98.6% *ee*) with the corresponding enyne–aldehyde precursors provided



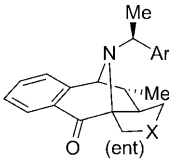
Scheme 2. Preparation of optically active hydroxylamine **1i**. a) NH_2OH·HCl, CH_2Cl_2; b) $NaBH_3(CN)$, MeOH; c) (*R*)-mandelic acid (MA) in *i*PrOH; d) 1 M NaOH (aq.); e) L-(+)-tartaric acid (TA) in EtOH.

Table 2. Scope of the hydroxylamine (**1i**)-directed [3+2] dipolar cycloaddition of azomethine ylides, generated in-situ from a gold-catalyzed cascade reaction.[a,b]

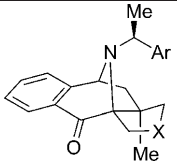
ntramolecular cycloaddition (X = $C(CO_2Et)_2$, Ar = *para*-nitrophenyl.



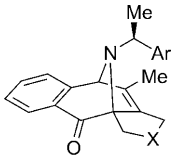
3ai 78 %
(98.5 % *ee*)



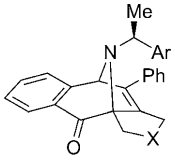
3bi 78 %
(96.4 % *ee*)[c]



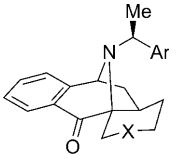
3ci 70 %
(95.4 % *ee*)



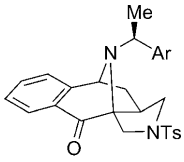
3di 67 %
(98.6 % *ee*)



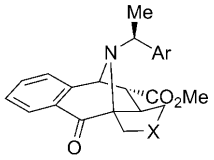
3ei 60 %
(98.6 % *ee*)



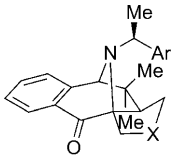
3fi 79 %
(97.6 % *ee*)



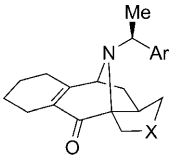
3gi 75 %
(97.5 % *ee*)



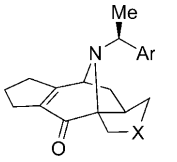
3hi 77 %
(96.7 % *ee*)



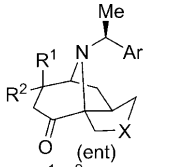
3ii 56 %
(96.7 % *ee*)



3ji 60 %
(98.6 % *ee*)

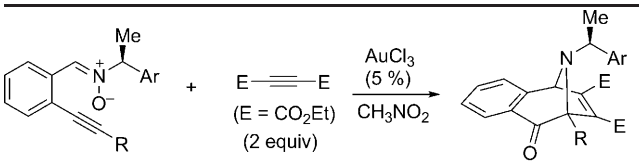


3ki 42 %
(96.7 % *ee*)



3li R^1,R^2 = $(CH_2)_5$
48 % (97.1 % *ee*)[c]

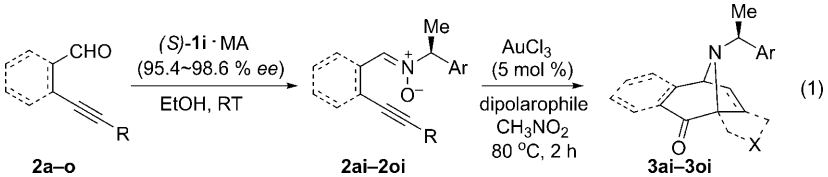
(intermolecular cycloaddition)



R	yield (d.r., % *ee*)
2mi H	**3mi** 45 % (1:1, 98.6 % *ee*)
2ni nBu	**3ni** 66 % (3:1, 96.5 % *ee*)[d]
2oi Ph	**3oi** 60 % (3:1, 96.5 % *ee*)[d]

[a] Optical purity of (*S*)-(+)-**1i** (95.4~98.6 % *ee*, Chiralcel OJ-H); % *ee* value refers to the **1i** used assuming the optical purity do not change (see text). [b] Reaction condition: [substrate] = 0.1 M in CH_3NO_2, 5 mol % of $AuCl_3$, 70 °C, 2 h. [c] Enantiomeric (*R*)-(−)-**1i** was used (ent). [d] The % *ee* of the major diastereomer.

the substrates for the intra- and intermolecular cycloaddition reactions [Equation (1), Table 2]. A series of tethered enynes, **2ai–2li**, containing various tether and dipolarophile groups, underwent a smooth reaction in excellent diastereoselectivity (typically > 90 % d.e.) and the respective single diastereomers of **3ai–3li** were isolated in good to moderate yields.[10] The optical purities in the products remained essentially unchanged from the starting (*S*)-(+)-**1i**·MA salt, as determined by HPLC analysis of **3ai** and **3di** (chiralcel OD column). The assignment of the relative and absolute stereochemistry of **3s** was based on the X-ray crystallographic data on **3ai** (Figure 2).



2a–o **2ai–2oi** **3ai–3oi** (1)

However, tri-substituted olefin substrate **2ii** and those devoid of an aromatic core (**2ji**–**2li**) led to lower yields. Notably, a longer tether (**3fi**, 79 %), an alkyl tether (**3li**, 48 %) and a nitrogen tether (**3gi**, 75 %) were also accommodated successfully. The intermolecular cycloaddition reaction was then attempted with **2mi–2oi** in the presence of diethyl acetylene dicarboxylate (2 equiv). Substrate **2mi**, which has a terminal alkyne group, showed poor diastereoselectivity. Interestingly, however, internal alkyne substrates **2ni** and **2oi** gave higher diastereomeric ratio of ca. 3:1.

From these data for the intra-/intermolecular cycloaddition reactions and the relative stereochemistry observed in Figure 2, we proposed the following model for asymmetric induction (Scheme 3): among the Felkin–Anh-type conformations of **E1–E3**,[5a] **E2** has a 1,3-allylic interaction between

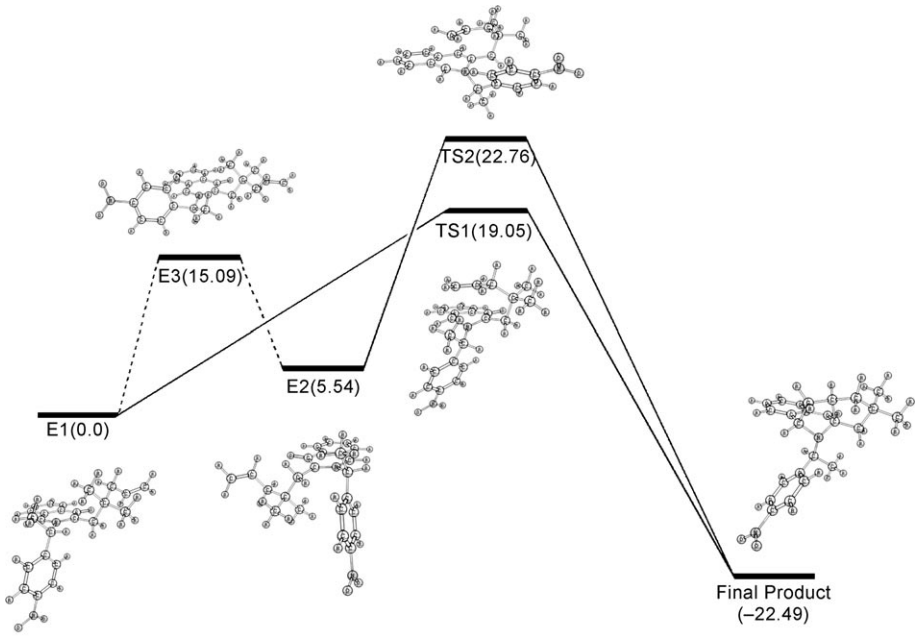
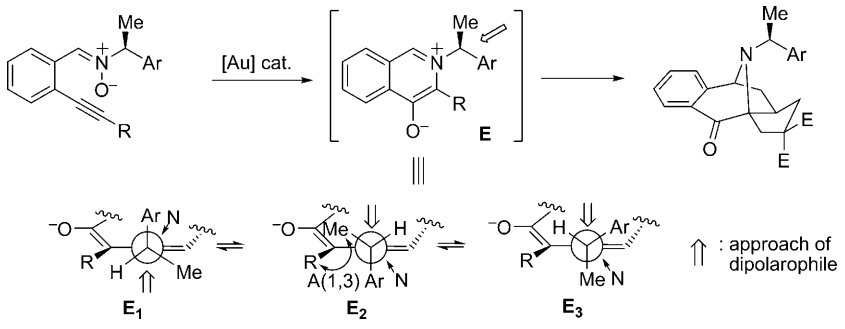


Figure 2. Potential energy surface diagram for the transformation of **E1** (and **E2/E3**) into the product.

the alkynyl substituent R and the methyl group on the auxiliary and thus should be disfavored relative to **E1**. The increase in diastereoselectivity from **3mi** to **3ni/3oi**, are in good agreement with this. To explain the observed increase in diastereoselectivity with decreasing aryl electron density on the auxiliary (Table 1), we propose that the electron density of electron-rich azomethine ylide is best stabilized when the electron-poor aryl group (C–Ar bond) is aligned perpendicular to the azomethine ylide as in **E1** (rather than **E3**), so that the σ^*_{C-Ar} orbital lies parallel to the π-orbital of azomethine ylide.[11] To support this explanation, we have conducted a DFT computational study using the Gaussian 03 program (B3LYP/6-31G(d) level).[12] For simplification, a simplified azomethine ylide was used analogous to those obtained with **2ai** ($X=C(CH_3)_2$ instead of $C(CO_2Et)_2$) with the gold-catalyst detached. As shown in Figure 1, the overall kinetic profile falls into Curtin–Hammet regime, where **E1** and **E2** equilibrates rapidly with **E3** as the transition state. The **TS1** (close to **E1**) has the lowest energy path ($\Delta\Delta H^{\neq}=$ 3.71 kcal mol^{-1} compared to **TS2** (close to **E2**)), en route to the final product (Table 3).

Table 3. Calculated energies of the ground and transition state conformers and the product.

Species	Absolute energy (hartree)	Relative energy (kcal mol^{-1})	No. of imaginary frequency
E1	−1265.301008	0.00	0
E2	−1265.292180	5.54	0
E3	−1265.276958	15.09	1
TS1 (E1)	−1265.270656	19.05	1
TS2 (E2)	−1265.264742	22.76	1
Final product	−1265.341622	−25.49	0



Scheme 3. Stereochemical rationale for the asymmetric induction.

Finally, we examined conditions for removing the *para*-nitrobenzyl auxiliary, as shown in Equation (2). Under hydrogenolysis conditions, the *para*-nitro group is initially converted into the aniline and in the presence of an additional benzylic C–N bond at the bridgehead carbon, the bond connecting the auxiliary could be selectively removed when treated with H_2 (balloon) and $Pd(OH)_2/C$ (20 mol% Pd) [Eq. (1)] to give **3a**. Alternatively, in the presence of Pd/C and 5 atm of H_2, the ketone could be reduced concomitantly, delivering amino alcohol **4a** (75%). Importantly, in the sequence of transformations (from **1i** to **3a/4a**) comprising nitrone condensation, tandem redox cycloaddition, and detachment of the auxiliary, no erosion of optical purity in the original **1i** (98.5% *ee*) could be detected.

In conclusion, we have reported an auxiliary-controlled asymmetric [3+2]-dipolar cycloaddition of azomethine ylide generated in-situ from gold-catalyzed redox reactions of nitronyl alkynes. We showed that electronically tuned hydroxylamine **1i** performed excellently as an auxiliary for the intramolecular cycloaddition by controlling the C–N rotation and was easily cleaved later under hydrogenolysis conditions. Further implications of **1i** to control rotamers in other dipolar cycloadditions, such as those of nitrones, are currently underway in our laboratory.

Experimental Section

$AuCl_3$ (1.5 mg, 0.0049 mmol) was added to a solution of nitrone (+)-**2ai** (50.0 mg, 0.0987 mmol, 98.6% *ee*) in nitromethane (1.0 mL). The resulting

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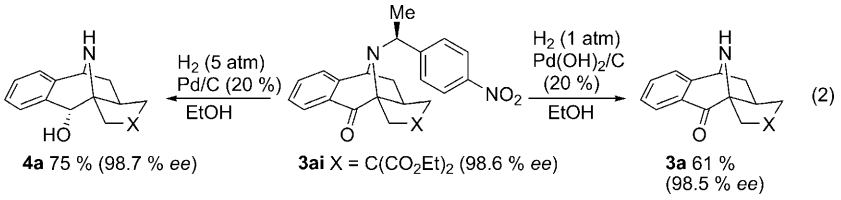

4a 75 % (98.7 % *ee*) **3ai** X = $C(CO_2Et)_2$ (98.6 % *ee*) **3a** 61 % (98.5 % *ee*)

mixture was heated at 70 °C for 1 h. The residue was concentrated to dryness and the resulting mixture was purified by column chromatography on silica gel (EtOAc/Hex = 1:4) to give 39.0 mg (78 %) of **3ai** as pale yellow solid ($[\alpha]_D^{23} = +162.5$ ($c = 1.21$, $CHCl_3$)).

Pd/C (0.20 equiv) was added to a solution of **3ai** (50 mg, 0.0987 mmol, 98.6 % *ee*) in EtOH (0.5 mL) and stirred under H_2 (5 atm) at RT for 12 h. The reaction mixture was filtered through a Celite pad and washed with MeOH and CH_2Cl_2. The solvent was removed and the residue was purified by column chromatography on silica gel (EtOAc/Hex = 2:1, 1 % MeOH) to give **4a** (26.6 mg, 75 %, $[\alpha]_D^{27} = +18.6$ ($c = 1.23$, $CHCl_3$)) as pale yellow solid. The optical purity of **4a** was measured by HPLC analysis to be 98.7 % *ee* on Chiralcel OD-H column (*n*-hexane: *i*PrOH = 97:3, 0.5 mL min^{-1}, $t_r = 22.2$ min for (+)-**4a** (major) and 30.2 min for (−)-**4a** (minor)).

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Keywords: [3+2] dipolar cycloaddition · chiral auxiliaries · gold · hydroxylamines · ylides

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[9] Assignment of the absolute stereochemistry of **1i** is based on the X-ray crystallography on **2i** (Figure 2, see the Supporting Information for details of the X-ray crystallographic procedure). Repeated recrystallization (x5) increased the enantioselectivity of (*S*)-(−)-**1i** to > 99 % *ee*.

[10] In cases where lower yields were obtained, the reaction was accompanied by unidentified decomposition products (observed in the crude ^{1}H NMR spectrum), possibly owing to the regio-isomeric redox process (e.g. to form isoindole and/or its decomposition by-products: see Ref. [3b]). However, these side-products were not the corresponding diastereomers, as indicated by the absence of the characteristic AB quartet pattern and the presence of messy olefinic resonances in the crude ^{1}H NMR spectrum. The desired isomer **3** was cleanly separated by column chromatography on silica gel in the indicated yields.

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