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Chiral Brønsted Acid Catalyzed Dynamic Kinetic Asymmetric Hydroamination of Racemic Allenes and Asymmetric Hydroamination of Dienes

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Abstract: *The first highly efficient and practical chiral Brønsted acid catalyzed dynamic kinetic asymmetric hydroamination (DyKAH) of racemic allenes and asymmetric hydroamination of unactivated dienes with both high E/Z selectivity and enantioselectivity are described herein. The transformation proceeds through a new catalytic asymmetric model involving a highly reactive π-allylic carbocationic intermediate, generated from racemic allenes or dienes through a proton transfer mediated by an activating/directing thiourea group. This method affords expedient access to structurally diverse enantioenriched, potentially bioactive alkenyl-containing aza-heterocycles and bicyclic aza-heterocycles.*

Dynamic kinetic asymmetric transformations (DyKATs) are a versatile and step-economical strategy for the synthesis of enantioenriched products with concomitant increase in molecular complexity from readily available racemic starting materials in a single step.[1] Over the past few decades, the synthetic advantages of DyKATs have been demonstrated using racemic substituted allenes. Given the intriguing features of the two cumulated C=C bonds and the peculiar axial chirality, racemic substituted allenes are highly valuable synthetic precursors for the straightforward synthesis of complex molecules.[2] In this field, several elegant transition metal catalyzed DyKATs of racemic unactivated allenes have been developed by the activation of the allenyl moiety through transition-metal coordination.[3] In sharp contrast, although asymmetric hydroamination of unactivated C=C bonds in alkenes, allenes, and dienes have been widely developed as an efficient way to prepare enantioenriched amines,[4] dynamic kinetic asymmetric hydroaminations (DyKAHs) that employ racemic allenes as substrates remain exceedingly scarce.[3b,e,5] In this aspect, only Widenhoefer et al. have reported a gold-catalyzed DyKAH of racemic trisubstituted allenes to form 2-vinyl pyrrolidine products with unsatisfactory *Z*/*E* ratios (2.0:1–10.1:1; Figure 1 a).[3b] Thus, the design and invention of conceptually different catalytic systems, especially with organocatalysts for DyKAHs of racemic unactivated allenes is highly desirable.

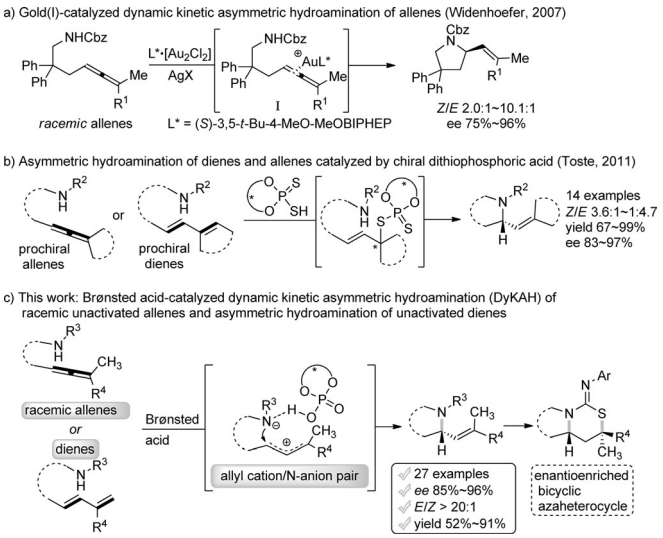

Figure 1. Dynamic kinetic asymmetric hydroamination (DyKAH) of racemic unactivated allenes and asymmetric hydroamination of unactivated dienes.

Chiral Brønsted acids, such as chiral phosphoric acids (CPAs), have recently evolved into a fundamentally significant tool for asymmetric catalysis.[6] Nevertheless, the activation of unactivated C=C bonds by a chiral Brønsted acid for nucleophilic attack[7] has been impeded by its inherently low basicity, and only recently have the group of List[7d] and our group[7c] independently disclosed highly enantioselective hydrofunctionalizations of unactivated alkenes using chiral imidodiphosphorimidate and phosphoric acid catalysts, respectively. Nonetheless, in this field, organocatalytic hydro-

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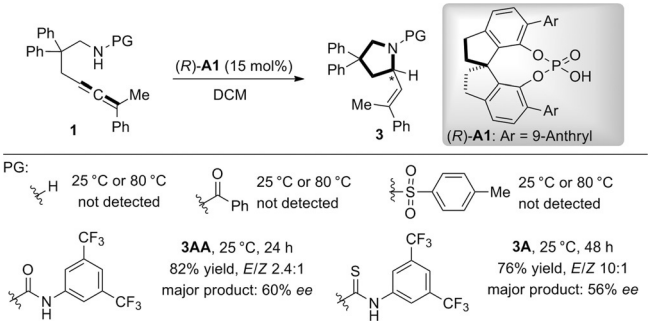
amination of allenes and dienes are still long-standing challenges that remain largely unsolved.[8] To date, only Toste et al. have reported enantioselective intramolecular hydroamination of dienes and allenes in the presence of chiral dithiophosphoric acids, by a transient covalently bound chiral leaving group on the allylic system, for excellent stereoinduction (Figure 1b).[7b,9] To address the challenges and inspired by those advances in activating alkenes with CPA, we became interested in developing an asymmetric Brønsted acid catalyzed hydroamination of C=C bonds. We hypothesized that a DyKAH of racemic *N*-(γ-allenyl) species could be achieved through an intramolecular proton transfer between an amine nucleophile and a racemic allene in cooperation with CPA to generate a π-allylic carbocationic intermediate, followed by an S_N1-type C–N bond formation to give the final azaheterocycle (Figure 1c). We further anticipated that such a key allylic cationic intermediate could also be generated from dienes, catalyzed by a chiral Brønsted acid, and might offer a new catalytic asymmetric hydroamination of unactivated dienes (Figure 1c).[4a,b,7b,9,10] Given the unique chemical properties of racemic unactivated allenes as well as the intrinsic instability and the high reactivity of the carbocationic intermediate, we envisioned several essential challenges that have to be overcome to realize this strategy,[9,11] including: a) how to efficiently generate the highly reactive π-allylic carbocationic intermediate from racemic unactivated allenes by a proton transfer catalyzed by CPA; b) how to promote the desired hydroamination reaction by the ion-pairing asymmetric catalysis;[6d,9,12] c) how to minimize the undesired deprotonation to generate dienes that lack sufficient reactivity;[13] d) how to achieve good discrimination between the enantiotopic faces of this π-allylic carbocation by electrostatic interactions that lack rigidity in the association.[6g,h,7d,11b,14] Herein, we disclose the first chiral Brønsted acid catalyzed DyKAH of racemic unactivated allenes and asymmetric hydroamination of unactivated dienes by ion-pairing asymmetric catalysis with excellent stereoinduction. The newly developed catalytic asymmetric hydroamination can deliver optically enriched azaheterocycles, which are being intensely investigated because of their high demand in the pharmaceutical industry (see Figure S1 in the Supporting Information).[15]

To probe the feasibility of our hypothesis, we set out to explore the effects of different N-protecting groups for their potential to efficiently participate in the Brønsted acid catalyzed DyKAH of racemic allenes in the presence of CPA in DCM (Table 1).[7c] Various allene substrates containing free amine, amide, and Ts-protected amine moieties failed to undergo the desired DyKAH. Fortunately, the use of the urea **1aa′** bearing two N–H bonds as the nucleophile gave desired product **3AA** in high yield, albeit with moderate enantioselectivity and *E*/*Z* selectivity. This proof-of-principle result encouraged us to further investigate other urea analogues to improve the stereoselectivity. Gratifyingly, the use of the thiourea substrate **1a** led to a remarkable improvement in *E*/*Z* selectivity (10:1) for **3A**.

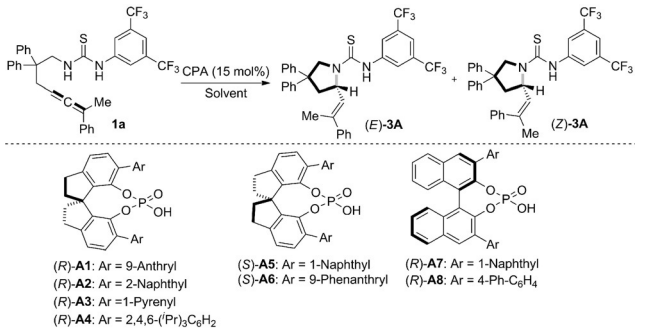
To improve the stereoselectivity, we then screened various SPINOL- and BINOL-derived CPAs (Table 2, entries 2–8) and found that (*S*)-**A5** gave both high *E*/*Z* selectivity and enantioselectivity (entry 5). A subsequent solvent screening indicated that solvent had a significant influence on the reactivity and stereoselectivity (entries 9–14), and PhCl was

Table 1: Evaluation of different protecting groups.[a,b]



[a] Yields are based on ^{1}H NMR analysis of the crude reaction mixture and the (*E*)-**3**/(*Z*)-**3** ratio was determined by ^{1}H NMR spectroscopy. [b] The *ee* values were determined based on HPLC analysis.

Table 2: Optimization of the reaction conditions for allene substrates.[a,b,c,d]



Entry	CPA	Solvent	Yield [%][b]	(*E*)-**3A**/(*Z*)-**3A**[c]	*ee* [%][d] (*E*)-**3A**
1	(*R*)-**A1**	DCM	76	10:1	−56
2	(*R*)-**A2**	DCM	58	13:1	−79
3	(*R*)-**A3**	DCM	64	6:1	−56
4	(*R*)-**A4**	DCM	17	7:1	−2
5	(*S*)-**A5**	DCM	64	13:1	83
6	(*S*)-**A6**	DCM	80	10:1	66
7	(*R*)-**A7**	DCM	6	–[e]	17
8	(*R*)-**A8**	DCM	12	–[e]	33
9	(*S*)-**A5**	DCE	64	10:1	75
10	(*S*)-**A5**	$CHCl_3$	60	6:1	56
11	(*S*)-**A5**	EtOAc	trace	–[e]	50
12	(*S*)-**A5**	CH_3CN	trace	–[e]	1.3
13	(*S*)-**A5**	THF	–[f]	–[f]	–[f]
14	(*S*)-**A5**	PhCl	78	20:1	86
15[g]	(*S*)-**A5**	PhCl	72	20:1	94
16[g,h]	(*S*)-**A5**	PhCl	70	20:1	91
17[i]	–	PhCl	–[f]	–[f]	–[f]

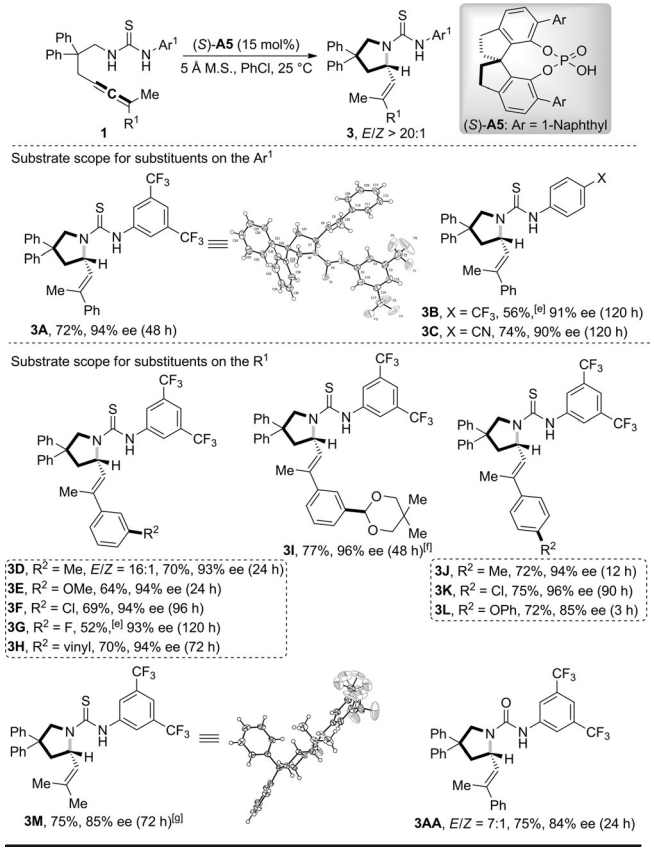
[a] Reactions were run on a 0.05 mmol scale in solvent (2.0 mL) at 25 °C for 48 h. [b] Yield based on ^{1}H NMR analysis of the crude reaction mixture. [c] Ratio of (*E*)-**3A**/(*Z*)-**3A** was determined by ^{19}F NMR analysis of the crude reaction mixture. [d] Measured by chiral-phase HPLC analysis. [e] Ratio was not determined. [f] Product was not detected. [g] 5 Å M.S. (50 mg) were used. [h] (*S*)-**A5** (10 mol%) was used. [i] No CPA catalyst. DCE = 1,2-dichloroethane, DCM = dichloromethane, THF = tetrahydrofuran.

identified as the most efficient solvent as it provided **3A** with excellent stereoselectivity (entry 14). The use of 5 Å molecular sieves as an additive further enhanced the stereoselectivity and thus, it gave the best result (entry 15). Further investigation revealed that lowering the catalyst loading to 10 mol% led to a slight decrease in yield and enantioselectivity (entry 16), and no desired product was detected in the absence of the CPA catalyst (entry 17).

With the optimal reaction conditions being established, we next explored the substrate scope of the DyKAH (Table 3). First, various substrates with different N-aryl groups all reacted smoothly to afford the corresponding products **3A–C** in 56–74% yields with 90–94% *ee* and excellent *E*/*Z* selectivity. The absolute configuration of **3A** was determined to be *S* by X-ray crystallography analysis (see Figure S2).[16] Next, diverse *N*-(γ-allenyl) thioureas bearing different substituents on the allenyl aryl rings, including electron-withdrawing (F or Cl) or electron-donating groups (OMe, Me, OPh, or vinyl) at different positions (*meta* or *para*), were found to be suitable substrates and afforded the expected products **3D–L** in 52–75% yields with outstanding *E*/*Z* selectivity and enantioselectivity, showcasing the excellent tolerance of substituents with distinct electronic properties. Importantly, the substrate **1h**, bearing a vinyl group that is often reactive in transition metal mediated transformations, was also converted into product **3H.** Notably, the acetal group was stable in the presence of the acidic catalyst despite the general acid lability of this protecting group, and **3I** was obtained with excellent results. Moreover, the protocol could be extended to an achiral allene with two terminal methyl groups, and the expected product **3M** (confirmed by X-ray study, see Figure S3) was obtained with good results. Additionally, *N*-(γ-allenyl) urea was also well-tolerated to give the expected product **3AA**. With the broad substrate scope, this approach constitutes an excellent alternative to the previously developed gold(I)-catalyzed DyKAH of racemic unactivated allenes.

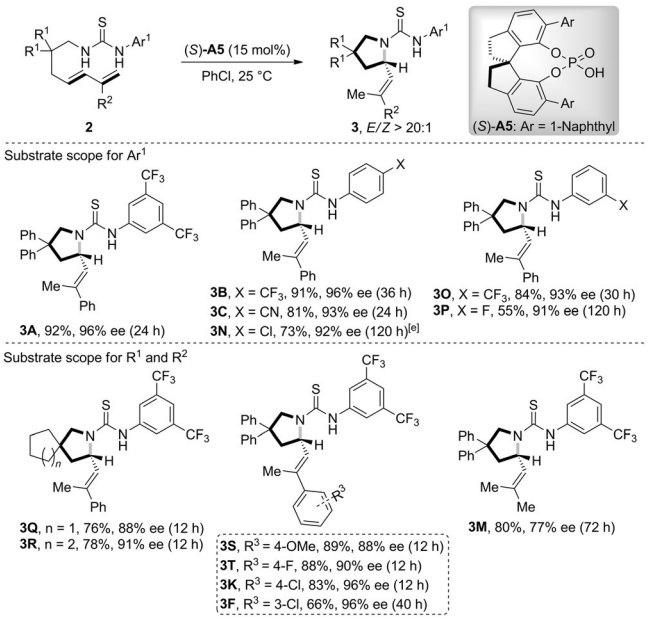
Next, we examined the hydroamination reaction of the *N*-(γ-dienyl) thiourea **2a** in the presence of (*S*)-**A1** (see Table S1).[7c] As expected, the reaction smoothly delivered the desired 2-vinyl pyrrolidine **3A** albeit with low *E*/*Z* selectivity (4:3). After considerable optimization efforts, (*S*)-**A5** was identified as the most efficient catalyst, providing (*E*)-**3A** in an almost quantitative yield with excellent enantioselectivity and *E*/*Z* selectivity (Table S1). Next, we investigated the scope of the catalytic asymmetric hydroamination of dienes (Table 4). Gratifyingly, the reaction of dienes having different N-aryl groups proceeded smoothly to provide the desired products **3A–C** and **3N–P** in 55–92% yields with 91–96% *ee*. We next explored the scope with respect to the tethers, and observed good tolerance of cyclic *N*-(γ-dienyl) thioureas containing five- to six-membered rings, affording the enantioenriched spiroproducts **3Q** and **3R** in high yields

Table 3: Substrate scope of the DyKAH of racemic allenes.[a,b,c,d]



[a] Reaction conditions: **1** (0.10 mmol), (*S*)-**A5** (15 mol%), and 5 Å molecular sieves (100 mg) in PhCl (4.0 mL) at 25 °C. [b] Yields of isolated products. [c] The *ee* values were determined by HPLC analysis. [d] The *E*/*Z* ratios were determined by ^{19}F NMR analysis of the crude reaction mixture. [e] Run at 35 °C. [f] Na_2SO_4 (100 mg) was added. [g] Using $CHCl_3$ (1.0 mL) as solvent and 5 Å molecular sieves (100 mg) and CG_{50} resin (100 mg) as additives.

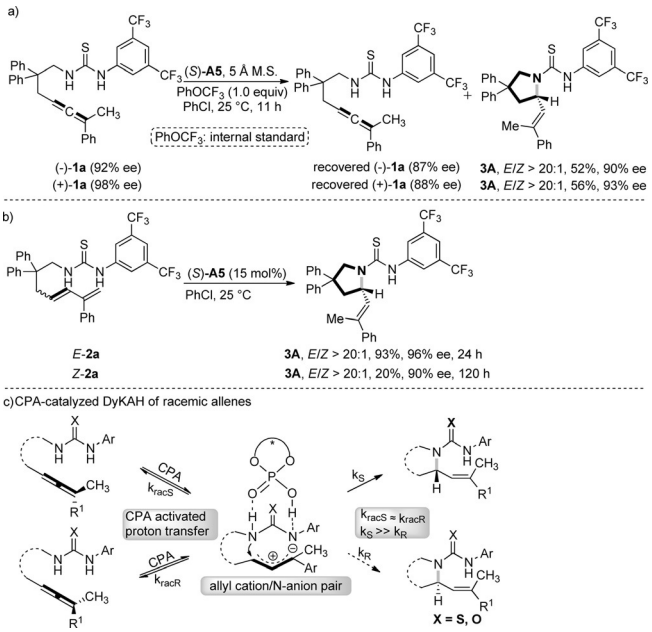
Table 4: Substrate scope of the asymmetric hydroamination of dienes.[a,b,c,d]



[a] Reaction conditions: **2** (0.10 mmol) and (*S*)-**A5** (15 mol%) in PhCl (4.0 mL) at 25 °C. [b] Yields of isolated products. [c] *E*/*Z* ratio was determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis. [e] Run at 30 °C.

with outstanding *ee* values. Meanwhile, we found that a variety of *N*-(γ-dienyl) thioureas with either electron-rich or electron-poor substituents on the allenyl aryl ring were viable substrates in this transformation to furnish the corresponding products **3F**, **3K**, **3S**, and **3T** in 66–89 % yields with 88–96 % *ee*. Additionally, it is striking to note that **2m**, possessing an allenyl methyl substituent, was also suitable for this reaction to give the expected product **3M**.

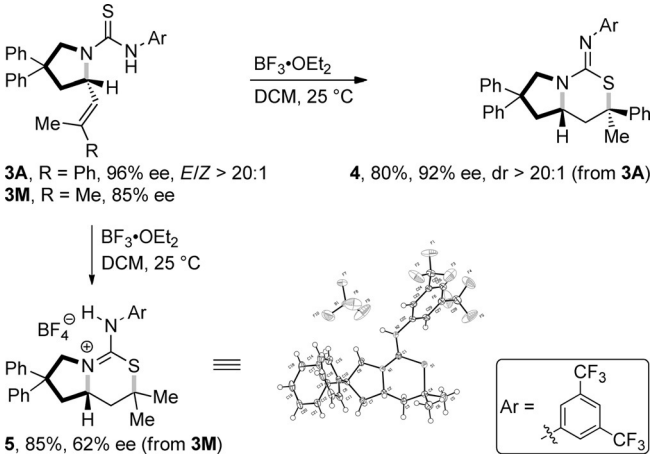
To gain insights into the reaction mechanism, some control experiments were conducted. First, to determine whether this catalytic stereoconvergent process was a DyKAH or not,[1d] we carried out asymmetric hydroamination reactions on the enantioenriched allenes (−)-**1a** (92 % *ee*) and its enantiomer (+)-**1a** (98 % *ee*). The hydroamination reactions proceeded at similar rates (see Figure S5), furnishing products (*E*)-**3A** with almost identical enantioselectivity (Scheme 1 a). We also observed similar racemization rates of



Scheme 1. Mechanistic study.

each enantiomer ($k_{racS} \approx k_{racR}$; Schemes 1 a and c). This result was similar to that in a previous report,[3b] indicating that the process might involve the formation of the same prochiral intermediate mediated by CPA[1d] and the formation rate of (*S*)-**3A** should be significantly higher than that of (*R*)-**3A** ($k_s \gg k_R$) in the presence of (*S*)-**5A** (Scheme 1 c). Furthermore, the lack of reactivity using an N-methyl thiourea (see Scheme S1), or Bz- or Ts-amides (Table 1) indicated that the thiourea bearing two N–H bonds might be essential for the effective activation and stereoinduction, as reported previously.[7c] Thus, the combined results favor a DyKAH mechanism, in which racemic allenes might bind to CPA to produce a prochiral π-allylic carbocation/N-anion pair during the enantioinduction process.[1d] In addition, (*Z*)- and (*E*)-**2a** showed significantly different reactivity, but almost the same stereoselectivity for asymmetric hydroamination (Scheme 1 b), supporting the involvement of the same π-allylic carbocationic intermediate. Based on the above mechanistic investigations and previous studies,[7c,d] we propose that the DyKAH of racemic unactivated allenes and asymmetric hydroamination of unactivated dienes proceed through a stepwise mechanism: the CPA forms hydrogen-bonding interactions with the thiourea moiety and thus, indirectly activates the C=C bonds to form the same π-allylic carbocation/N-anion pair by an intramolecular proton transfer,[17] followed by an S_N1-type C–N bond formation to give the final product (Scheme 1 c and Figure 1 c).

To demonstrate the synthetic utility of the current protocol, we treated the products **3A** and **3M** with $BF_3{\cdot}OEt_2$ to straightforwardly obtain the bicyclic aza-heterocycles **4** and **5**, respectively, bearing new quaternary stereocenters in high yield (Scheme 2). The structure of **5** has been unambiguously determined by X-ray structural analysis (see Figure S4).



Scheme 2. Transformations of **3A** and **3M**.

In summary, a chiral Brønsted acid catalyzed DyKAH of racemic unactivated allenes and asymmetric hydroamination of unactivated dienes with both excellent *E*/*Z* selectivity and enantioselectivity have been developed. Significantly, this new catalytic asymmetric hydroamination strategy involves a highly reactive π-allylic carbocationic intermediate generated from either the racemic allenes or dienes by an intramolecular proton transfer, and invokes cooperative multiple hydrogen-bonding interactions between the reacting thiourea group and Brønsted acid. This protocol could serve as a good complementary approach to the conventional metal-catalyzed DyKAH of racemic allenes and asymmetric hydroaminations of dienes, providing expedient access to a diverse range of enantioenriched alkenyl-containing aza-heterocycles and bicyclic aza-heterocycles. Further studies to expand the scope and to develop the more challenging intermolecular DyKAH of racemic allenes with this strategy are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allenes · Brønsted acids · dienes · heterocycles · hydroamination

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[16] CCDC 1886907, 1886903, and 1887492 (**3A**, **3M**, **5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[17] See Scheme S2 for an alternative possible reaction pathway suggested by a reviewer.

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