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Synthetic and Mechanistic Study of the Catalytic Enantioselective Preparation of Primary β-Amino Ketones from Enones and a Fluorinated Gabriel Reagent

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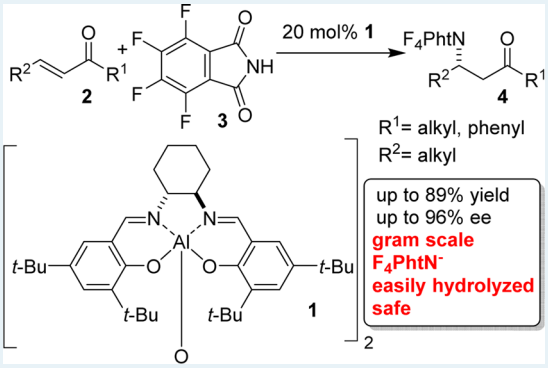
Supporting Information

ABSTRACT: The salen μ-oxo complex of aluminum **1** catalyzes the asymmetric 1,4-addition of the novel ammonia equivalent 3,4,5,6-tetrafluorophthalimide to unsaturated ketones. All of the reagents are inexpensive and are readily available. The products are formed in up to 89% yield and up to 96% ee. The tetrafluorophthalimide group is removed under mild chemoselective conditions and in high yields to afford the free primary amines. Mechanistic studies suggest that the reaction occurs through a dual activation mechanism. A pre-equilibrium formation of a 1:1 complex between tetrafluorophthalimide and the catalyst is observed. The rate-determining step is the addition of tetrafluorophthalimide catalyst complex to the catalyst activated enone. These mechanistic studies provide important clues for the further development of catalytic asymmetric reactions.



KEYWORDS: *ammonia equivalent, β-amino ketones, aza-Michael addition*

INTRODUCTION

Enantiopure primary β-amino ketones are of great utility in the synthesis of drugs and natural products.[1] However, the synthesis of chiral primary (RNH_2) β-amino ketones remains a challenge. Chiral β-amino ketones may be prepared by catalytic asymmetric Mannich reactions and aza-ene reactions;[2−4] however, these methods rely on precursors prepared in multistep sequences. A highly attractive alternative is the aza-Michael addition reaction, since it makes use of simple and readily available enones **2** as the starting material.[5] While there have been many reports on the asymmetric addition of nitrogen heterocycles to enones, these methods do not offer access to primary β-amino ketones.[6−9] Indeed, the preparation of β-amino ketones through the aza-Michael addition of a suitable masked ammonia equivalent to an enone appears to be the most challenging of all (see below).

Consequently, there are only a few comparable reports in the literature.[10−12] One approach toward this problem relies on amine catalysis. Deng reported the use of N-Boc-OBn-substituted hydroxylamines as nucleophiles in the aza-quinine (20 mol %) and TFA (40 mol %) catalyzed aza-Michael addition to simple enones (Scheme 1).[10,12,13] The N−O bond was cleaved with Raney nickel,[10] conditions that are incompatible with many common functional groups. Furthermore, the protected hydroxylamine derivatives must be prepared in two steps prior to the aza-Michael addition, and an additional step is needed to remove the Boc group and reveal the primary amine. Earlier work used *O*-benzylhydroxylamine as the nucleophile, but the enantioselectivity was generally below 60%.[10b] Wang recently reported the use of 4-nitrophthalimide as the nucleophile and replaced the TFA used by Deng with 4-chlorobenzoic acid to give the corresponding protected amino ketones in yields of 51−98% and generally high ee values.[10c] Hydrazine derivatives may be another alternative,[14] but the aza-Michael addition products were transformed into heterocyclic compounds and not β-amino ketones. A conceptually different approach is based on Lewis acid catalysis. Shibasaki reported the use of *O*-methylhydroxylamine as the nucleophile and the BINOL alkoxide derived catalyst $YLi_3(BINOL)_3$ (1−3 mol %).[10] The products were formed in high yields and enantiopurities with reaction times of 2−6 days.

Jacobsen reported the use of HN_3 as an ammonia equivalent in the catalytic enantioselective conjugate addition to simple unsaturated ketones **2** with 61−94% ee using the inexpensive and readily available chiral salen-Al μ-oxo complex **1** (5 mol %) as the catalyst.[11,15,16] However, HN_3 is known to be explosive and highly toxic. Moreover, it is recommended that the product azides be handled with great caution.[17] The extensive efforts expended in finding an azide-free synthesis of the important antiviral agent tamiflu serve as a powerful illustration of this issue.[18]

We were interested in developing an alternative method that would give access to protected amino ketones from readily

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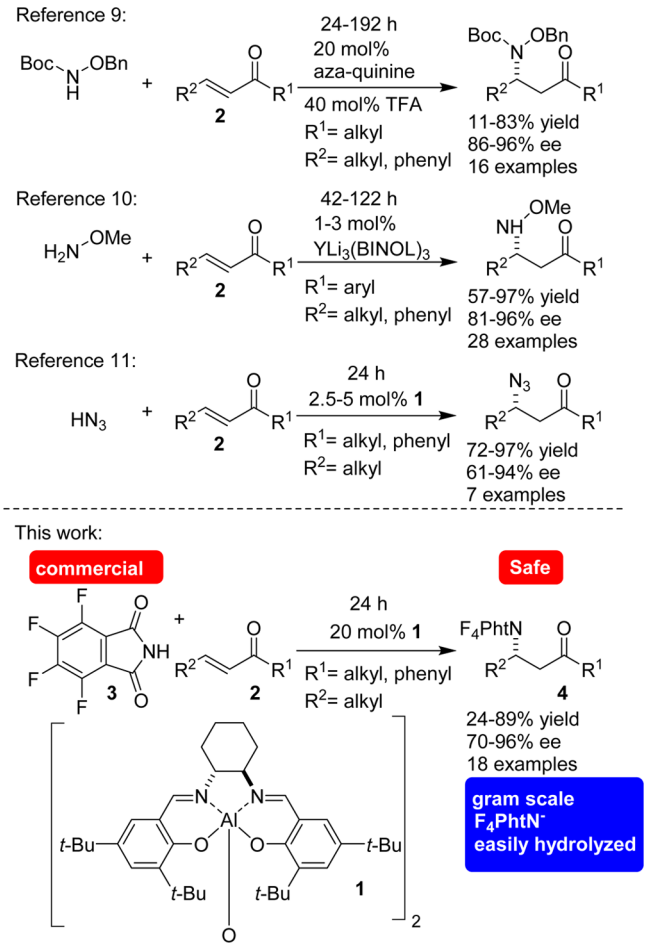
Scheme 1. Comparison of Methods



available[4] α,β-unsaturated ketones, while avoiding the use of hazardous or expensive reagents and products and still allowing chemoselective deprotection of the amine. Furthermore, we desired to understand this reaction in depth, since mechanistic insight could provide valuable information as to how these reactions proceed and clues to how to improve them.

Herein, we report a highly enantioselective synthesis of amino ketones **4** from enones **2** and 3,4,5,6-tetrafluorophthalimide (TFP; **3**) as a safe, novel nucleophilic ammonia equivalent and protecting group (Scheme 1). The reaction is carried out at room temperature to give the products in yields up to 89% and up to 96% ee. Many of the products are crystalline, allowing the ee to be increased by recrystallization. The tetrafluorophthalimide group may be removed under mild chemoselective conditions and in high yield without any detectable loss of enantiomeric purity to reveal the primary amine. Furthermore, we report mechanistic studies that reveal that this reaction takes place through activation of both the nucleophile **3** and the enone **2** by catalyst **1**. A mechanism is proposed, and several important lessons pertinent to aza-Michael additions are revealed.

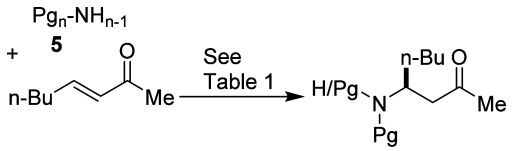
In the analysis of our reaction design, several potential pitfalls presented themselves. First, inhibition of the catalyst by the nitrogen nucleophile or the product would lead to low reaction rates and long reaction times or required high catalyst loadings. Indeed, catalyst loadings in aza-Michael reactions are generally high (10–20 mol %). The observation that the reported Lewis acid catalyzed addition of carbamates to pinacolone-derived ketones required up to 6 days may be a manifestation of such effects.[19] In the work by Shibasaki[10] lower catalyst loadings (1–3 mol %) could be used but reaction times of 2–5 days were recorded.

Additionally, in order to avoid product polymerization via imine- and enamine-type chemistry, the nucleophile must be a protected ammonia equivalent rather than ammonia itself. Naturally, the protection group must be subsequently cleavable in a high-yielding, facile manner.

RESULTS AND DISCUSSION

In the initial stage of our work, we investigated several different potential ammonia equivalents (**5**) as nucleophiles in the addition to enone **2a** (Table 1). We also screened several chiral

Table 1. Identification of a Suitable Nucleophile[a]



2a **4**

entry	conditions	nucleophile	*t*	yield/ee (%)[a,b]
1	**1** (20 mol %), toluene, room temp	*o*-$NO_2PhSO_2NH_2$	3 days	45
2	**1** (20 mol %), toluene, room temp	*p*-$CF_3PhSO_2NH_2$	12 days	44
3	**1** (20 mol %), toluene, room temp	*p*-$CNPhSO_2NH_2$	3 days	13
4	**1** (20 mol %) toluene, room temp	$C_6F_5SO_2NH_2$	3 days	38
5	**1** (20 mol %) toluene, room temp	$CF_3SO_2NH_2$	3 days	81
6	**1** (20 mol %) toluene, room temp	CF_3CONH_2		no reaction
7	**1** (20 mol %) toluene, room temp	PhthNH	12 days	27
8	**1** (20 mol %) toluene, room temp	TFP (**3**)	24 h	48
9	**1** (20 mol %) toluene, room temp[c]	TFP (**3**)	24 h	75/82
10	**1** (20 mol %) hexane, 4 Å MS, room temp[c]	TFP (**3**)	24 h	82/84

[a]Isolated yield after flash chromatography. [b]Determined by HPLC analysis. [c]1.2 equiv of ketone and 1 equiv of TFP.

salen-derived Lewis acid catalysts, with the aluminum salen μ-oxo complex **1** in toluene as the solvent consistently working best. Other salen complexes, e.g. salen-Al-Me, did not catalyze the reaction. A 1:1.2 molar ratio of ketone to nucleophile was used in these experiments. We postulated that the acidity of the protected ammonia equivalent would be crucial, as catalyst turnover would necessarily involve a proton transfer step. Accordingly, our first choice for a nitrogen nucleophile was the Fukuyama *o*-nosyl amide ($pK_a \approx 10$),[20] a known nucleophile in Mitsonobu reactions (Table 1, entry 1).[21] Other electron-deficient sulfonamides were also tested (entries 2–4); in all cases the desired products were obtained in low yields (13–45%), even after extended reaction times (3–12 days). Triflic amide (Table 1, entry 5) was a more effective nucleophile, providing the adduct in 81% yield after 3 days. However, the absence of efficient methods for the hydrolysis of triflic amides

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in combination with the slow reaction rates precludes it as a viable ammonia equivalent.

Turning to carboxamide nucleophiles, we found that trifluoroacetamide (Table 1, entry 6) does not add to **2a** (<2% conversion). We considered phthalimide (pK_a = 8.3) because of its use as an ammonia equivalent in the venerable Gabriel method. Nonetheless, as shown in entry 7, the reaction efficiency was not improved. We then examined the analogue 3,4,5,6-tetrafluorophthalimide (**3**; TFP), which is commercially avilable as a crystalline solid and has a pK_a of 5.3. Indeed, TFP (**3**) was seen to add to ketone **2a** and afford the product in 48% yield after 24 h (Table 1, entry 8). This result was further pursued due to the high rate of addition and the stability of the protected product under the reaction conditions, as well as in various acidic and basic media.

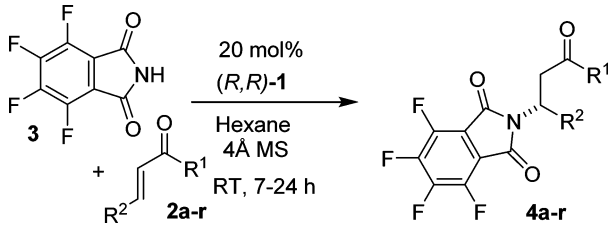
When the reaction was performed with 1.2 equiv of the ketone, the yield of the product improved to 75% (Table 1, entry 9). An analysis of the products by HPLC was carried out against authentic, racemic products.[22] A number of different solvents were screened to optimize the yield and enantioselectivity (see Table S1, Supporting Information). In dichloromethane and acetonitrile, poor conversion (<10%) was observed. The transformation proceeded to full conversion in diethyl ether and THF, albeit in lower enantioselectivity (67 and 72% ee, respectively). In hexane in the presence of molecular sieves (4 Å), the product was obtained in 82% yield and 84% ee (Table 1, entry 10). The latter conditions were chosen for further investigation.

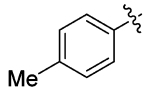
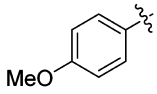
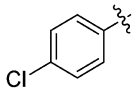
We then examined the scope with respect to the enone **2** (Table 2). The reaction is tolerant of both alkyl and aryl groups in the R^1 position, as well as alkyl groups in the R^2 position. Reaction times ranged from 7 to 24 h. Remarkably, even sterically hindered substituents, such as isopropyl (Table 2, entry 11) or cyclohexyl (entry 13), are tolerated in the R^2 position, despite their proximity to the unsaturated acceptor carbon. Incredibly, even *tert*-butyl-substituted enones **2o−r** are tolerated as substrates in the reaction (entries 15−18), although reaction times increased to 3 days. The absolute configuration of **4q**, prepared using catalyst *R,R*-**1**, was unequivocally determined by X-ray crystallography to be in the *S* configuration. The X-ray data of **4q** are included in the Supporting Information.

To illustrate the practicality of the method, we performed a representative reaction: namely, the preparation of **4c** on gram scale. While the product yield slightly diminished (65%), the enantioselectivity (82% ee) was not affected. Moreover, the enantiopurity of amino ketone **4d** may be increased up to 96% by a single recrystallization from ethyl acetate/hexane. Indeed, many of the products **4** prepared herein are crystalline due to the TFP group, allowing an increase in the product enantiopurity by simple recrystallization.[22]

To showcase the utility of TFP (**3**) as a practical ammonia equivalent, we have developed a set of mild conditions for deprotection (Scheme 2). First, the ketone was protected to prevent imine formation and polymerization after amine deprotection. Accordingly, the reaction of ketone **4c** (84% ee) with PTSA and 1,3-propane diol at reflux gives acetal **6** in 82% yield. Subsequently, tetrafluorophthalimide was removed by hydrazine monohydrate in methanol at 65 °C to give free amine **7** in quantitative yield.[23] These deprotection conditions are compatible with virtually all common functionalities, including TBS- and TES-protected alcohols, benzyl-protected phenol, lactones, and even *β*-lactams in some cases.[24] To confirm that the deprotection sequence did not adversely affect the enantiopurity, amine **7** was converted into its benzoic amide and analyzed by HPLC. The starting amino ketone **4c** and the benzoic amide of **7** were both obtained in 84%

Table 2. Scope of the Reaction[a]



Entry		R^1	R^2	Yield[a] (%)	ee[b] (%)
1	**4a**	Et	Me	82	86
2	**4b**		Me	86	89
3	**4c**	Me	*n*Bu	82	84
4	**4d**	Me	*n*Pent	77	77
5	**4e**	Me	*n*Nona	79	76
6	**4f**	Me	*n*Hept	83	84
7	**4g**	Me	$PhCH_2CH_2$	75	70
8	**4h**	Me	$(CH_3)_2CHCH_2$	89	82
9	**4i**		*n*Hept	54	96
10	**4j**		*n*Nona	79	93
11	**4k**		*i*Pr	70	89
12	**4l**		$PhCH_2CH_2$	82	80
13	**4m**			24	97
14	**4n**	Me	TBS-OCH_2CH_2	85	73
15[c]	**4o**		*t*Bu	68	86
16[c]	**4p**		*t*Bu	66	87
17[c]	**4q**		*t*Bu	55	90
18[c]	**4r**		*t*Bu	69	88

[a]Isolated yield after flash chromatography. [b]Determined by HPLC analysis. [c]Reaction time 24 h.

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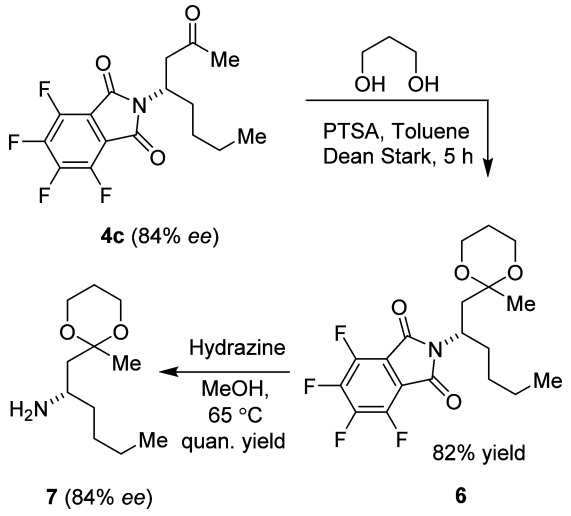
Scheme 2. Deprotection of β-Amino Ketone 4c



enantiomeric excess, underscoring the stability of the stereogenic center of β-tetrafluorophthalimido ketone under acidic conditions and at high temperature.

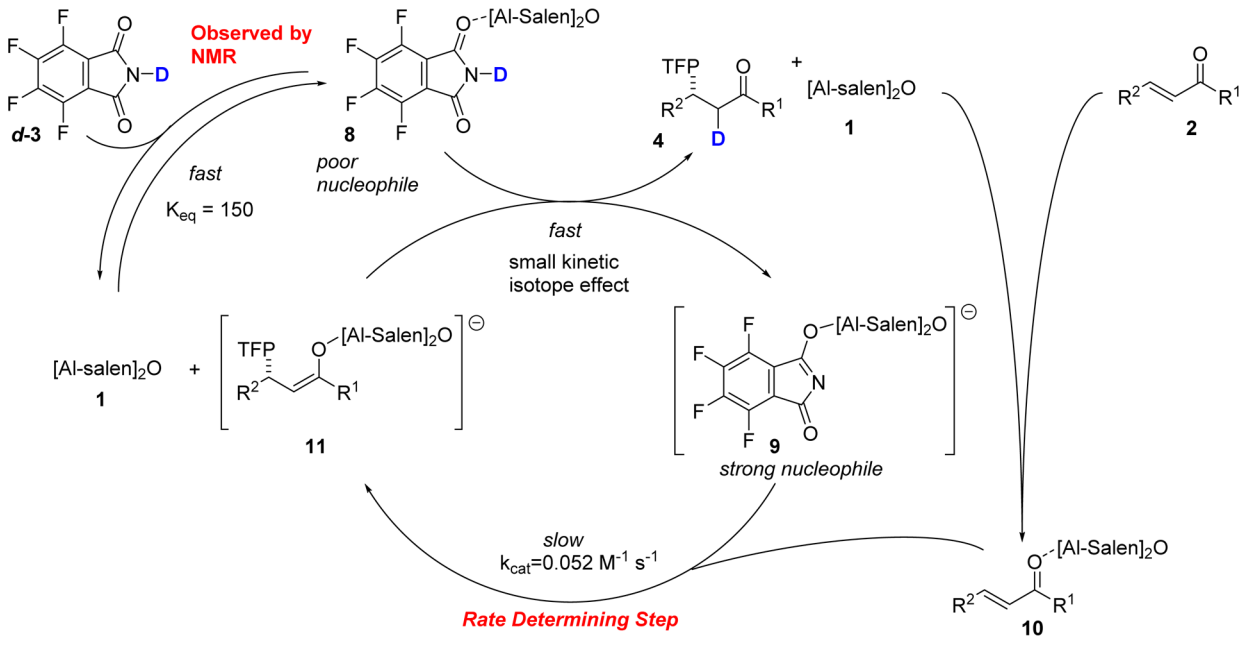
We studied the kinetics of the reaction of **2d** to afford **4d**, in order to elucidate the mechanism (Scheme 3).[25] The reaction showed a first-order dependence on the concentration of the enone within the studied range of concentrations (Figure 1b). For TFP (**3**), the reaction showed saturation kinetics under the reaction conditions (0.0833 M, Figure 1a). A ^{1}H NMR spectrum measured immediately upon mixing of the reagents revealed the formation of the TFP catalyst complex **8** (Scheme 3), which was characterized by NMR (Figure S1, Supporting Information).[22] This new complex is generated almost instantaneously, and its concentration diminishes relatively slowly over the course of the reaction (Figure 2, purple trace, and Figure 3, trace c). As the complex is consumed, free **1** is regenerated (Figure 2, green trace, and Figure 3, trace e).[22] The equilibrium constant for the association of TFP (**3**) to the catalyst **1** to give **8** was determined to be 150 ± 20 M^{-1} at 25 °C.[22] At a 5:1 ratio of **3** relative to **1**, similar to the ratio at the beginning of the reaction, no free aluminum μ-oxo salen complex **1** could be observed by NMR. In these experiments the ratio of **3** to **1** in complex **8** was found to be 1:1. This was confirmed from experimental data used to generate the representative Job plot (Figure 4).[26] The maximum value in this plot is seen at 0.544 rather than 0.50, possibly reflecting that the bimetallic catalyst **1** may coordinate to two molecules at TFP at high ratios of TFP to catalyst. Collectively, these observations support a fast, prerate-determining-step equilibrium to form **8** (Scheme 3). In addition, slow formation of minor amounts of an unidentified complex over the time of the reaction is observed (Figure 3, trace d).[22] On the basis of NMR this appears to be a degradation product of the catalyst.

A reaction progress kinetic analysis was carried out (Figure 5, red plot), and the results were further analyzed.[27] No product inhibition could be observed when 20 mol % of the product was added to the reaction mixture (Figure 5, green plot). In contrast, the reaction using an excess of 25 mol % of TFP (**3**), i.e. 1.25 equiv, led to a significant lowering of reaction rate (Figure 5, blue plot). This is consistent with TFP competing for binding to the catalyst with enone **2**, further suggesting that TFP has a higher affinity for catalyst **1** than enone **2**. The enone activation is not the rate-determining step, as this would result in first-order behavior of the catalyst in solution.

Inhibition of the reaction at high TFP concentrations is also consistent with the data in Figure 1a, where the reaction rate can be seen to drop at TFP concentration >0.1 M. Unfortunately, higher concentrations of TFP could not be examined, due to its low solubility in toluene. This observation also explains why the reaction is best carried out with a slight excess of enone **2** in comparison to TFP **3** (see above).

A deuterium labeling experiment was carried out by using deuterated TFP ***d*-3** (Scheme 3). No significant change in rate was observed, as the rate was ca. 0.8 relative to the regular reaction. This indicates that N−H bond breaking and thus

Scheme 3. Plausible Mechanism of the Reaction (Shown for *d*-3)



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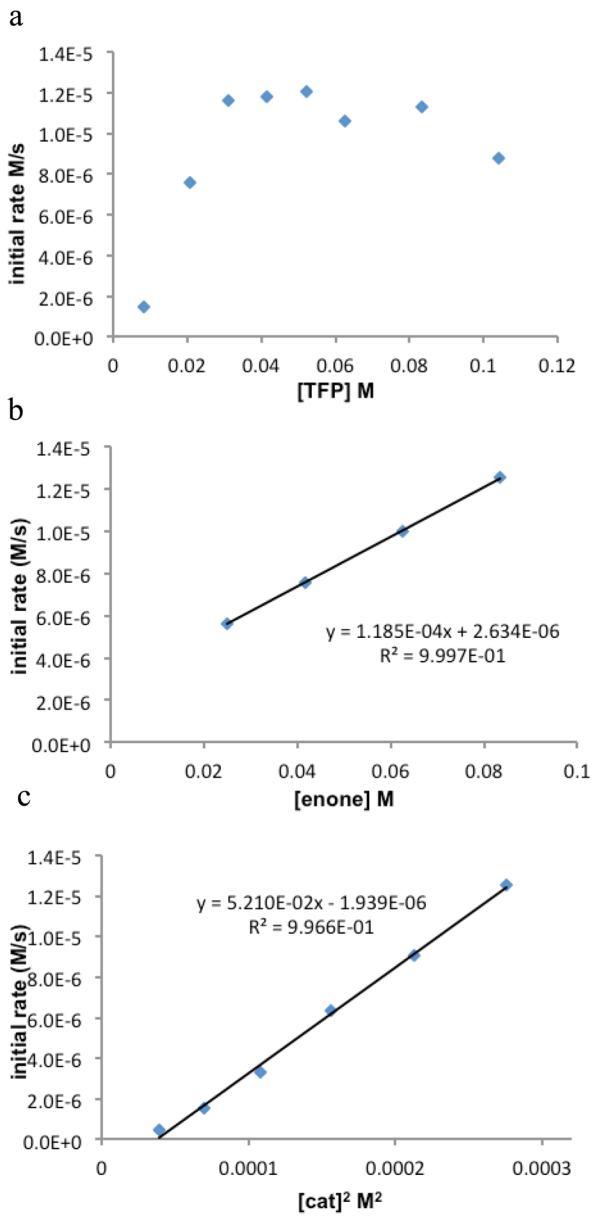

Figure 1. Initial rate dependence on the concentration of (a) tetrafluorophtalimide (**3**), (b) enone **2d**, and (c) catalyst **1**.

proton transfer is not the rate-determining step of the reaction.[22]

Since the reaction is second order in catalyst, the catalyst must activate both TFP (**3**), as observed, while a second molecule activates another species in the reaction. As the protonation step has been ruled out experimentally as being the rate-determining step and enone activation only would be first order in catalyst, this leads to the conclusion that the rate-determining step must be the addition of either TFP catalyst complex **8** or the analogue **9** to the enone catalyst complex **10** presumably to give the classical conjugate addition enolate **11**, as shown in Scheme 3. The resulting enolate is then rapidly protonated to liberate product **4** and free catalyst **1**. We propose that the proton source is the poorly nucleophilic but highly Brønsted acidic complex **8**, which after deprotonation forms the more nucleophilic complex **9**. This is in agreement with the low kinetic isotope effect observed. A positive nonlinear effect was found (Figure 6), further supporting a

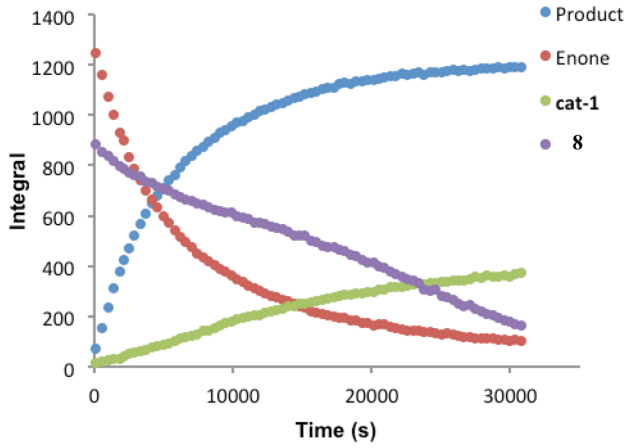

Figure 2. Representative reaction profile over 8.5 h. The reaction was followed by ^{1}H NMR (see Figure 3). Reaction conditions: [**1**] = 0.0166 M, [**2d**] = 0.0833 M, [TFP (**3**)] = 0.0833 M at 268 K, in toluene-d_8.

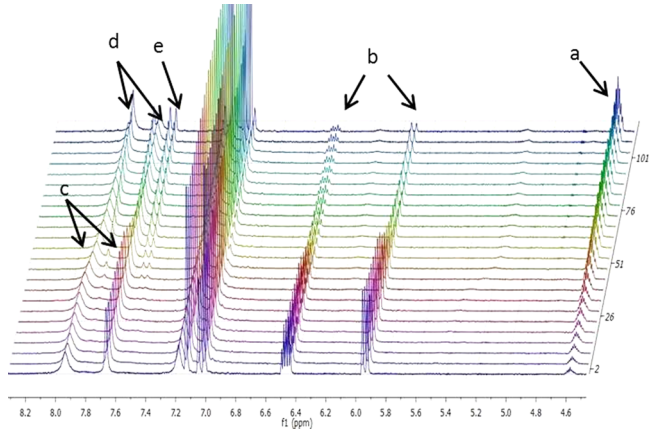

Figure 3. Reaction progress over 8.5 h as followed by ^{1}H NMR in d_8-toluene: (a) product **4d**; (b) starting material **2d**; (c) TFP catalyst complex **8**; (d) catalyst degradation product; (e) free catalyst **1**.

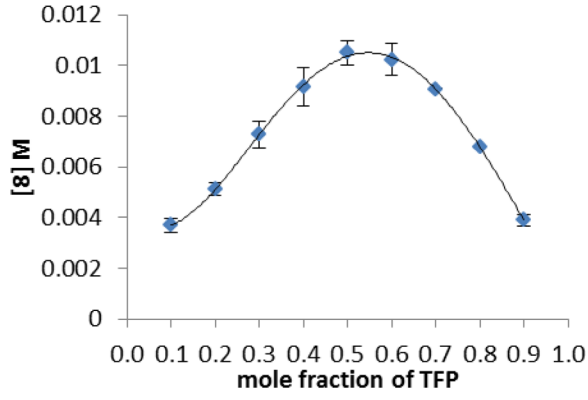

Figure 4. Job plot of the TFP catalyst complex **8** with a maximum at 0.544 indicating a 1:1 complex.

rate-determining step involving two molecules of catalyst, as shown in Figure 1c.

The TFP inhibition of the reaction by binding to catalyst **1** explains both the superior conversion obtained using 1.2 equiv of the enone as well as the finding that 20 mol % of catalyst is needed. Indeed, at 10 mol % catalyst loading, the reaction rate

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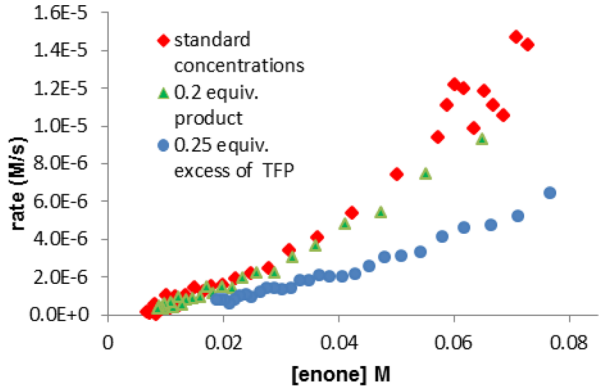

Figure 5. Reaction progress at a **3**:**2d**:catalyst (**1**) ratio of 1:1:0.2 (red), with 20 mol % of the product added (green), and at a ratio of 1.25:1:0.2 (blue).

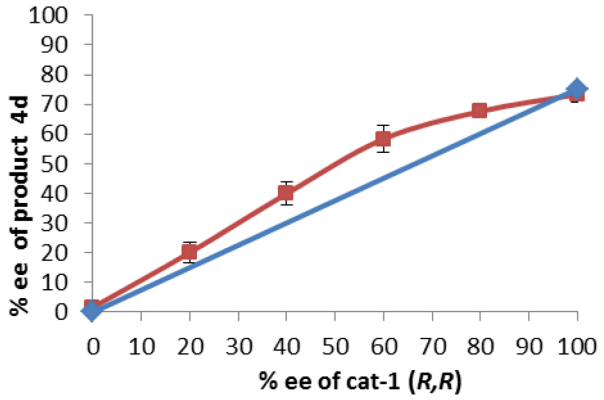

Figure 6. Nonlinear effect of the reaction among **3**, **2d**, and **1**.

is extremely slow and the reaction does not go to completion. At these concentrations, the amount of catalyst **1** available for activating the enone is negligible; this leads to low rates, and eventually, conversion is arrested if the catalyst is deactivated by e.g. water before complete conversion is achieved. Importantly, this finding also provides a clue as to how to achieve an aza-Michael addition with lower catalyst loadings. If a catalyst can be found with a propensity toward selective binding to the enone, catalyst loadings could be lowered significantly. However, since nitrogen nucleophiles are naturally Lewis basic and hence should be expected to bind to Lewis acids, an approach involving the use of one catalyst to bind and activate the nitrogen nucleophile and a second with better binding to the enone would likely be more fruitful. This should be true in all catalytic asymmetric reactions involving nitrogen nucleophiles. Indeed, one might speculate that this is the reason there are many more examples of aza-Michael addition to more Lewis basic unsaturated imides, amides, and esters than there are to enones. Additionally, this may also be the reason aza-Michael additions utilizng nitrogen heteroaromatic nucleophiles of relatively low basicity are successful.

CONCLUSIONS

We have developed a practical catalytic enantioselective conjugate addition of tetrafluorophthalimide (**3**) to unsaturated ketones (**2**) as a novel preparation of β-amino ketones. Reactions generally afford the products in high yields and excellent enantioselectivity of up to 96%. The present report outlines the first example of tetrafluorophthalimide (**3**) as a masked amine and indicates that it may be applied in other settings. The method provides a safe and valuable alternative to the methods requiring HN_3. The tetrafluorophthalimide protection group can be hydrolyzed in quantitative yield to reveal the free amine without adverse effects on ee or overall yield.

The reaction is second order in catalyst, consistent with a mechanism in which both enone and tetrafluorophthalimide are activated by the Lewis acid catalyst. Significantly, the strong ability of TFP and other nitrogen nucleophiles to bind to the catalyst explains why they inhibit the reaction. Our mechanistic studies thus point to a potential solution to achieve lower catalyst loadings in reactions involving nitrogen nucleophiles, namely dual catalysis. Research in this direction is currently underway and will be reported.

ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/cs501744e.

Synthetic procedures, characterization data, mechanistic and kinetic data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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