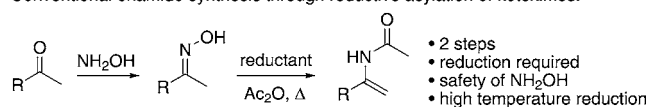**Enamide Synthesis**

Direct Titanium-Mediated Conversion of Ketones into Enamides with Ammonia and Acetic Anhydride
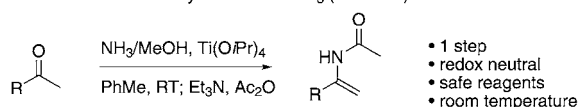
Jonathan T. Reeves, Zhulin Tan, Zhengxu S. Han, Guisheng Li, Yongda Zhang, Yibo Xu, Diana C. Reeves, Nina C. Gonnella, Shengli Ma, Heewon Lee, Bruce Z. Lu, and Chris H. Senanayake*

N-Acyl enamides are useful compounds in organic synthesis. In the realm of catalytic asymmetric hydrogenation, they are among the most exhaustively studied class of substrates, and provide access to valuable chiral amine building blocks.[1] These substrates have also demonstrated broad utility in catalytic asymmetric C−C bond forming processes such as aza–ene,[2] Michael,[3] Friedel–Crafts,[4] cycloaddition,[5] and arylation[6] reactions. Despite the extensive applications of *N*-acyl enamides, their preparation remains challenging. The direct condensation of acetamide with ketones, while attractive in its simplicity, proceeds either in low yields or not at all for the majority of ketone substrates.[7] The Pd-catalyzed cross-coupling of vinyl electrophiles with amides[8] and the Heck reaction of *N*-vinylacetamide with aryl halides[9] often require additional steps for preparation of coupling precursors and employ a costly transition metal catalyst.[10] The addition of alkyl magnesium or alkyl lithium reagents to nitriles followed by trapping with Ac_2O or AcCl has limited functional-group tolerance[11] and requires low reaction temperatures.[12] By far the most commonly employed procedure is the two-step conversion of ketones through ketoximes (Scheme 1).[13]

Conventional enamide synthesis through reductive acylation of ketoximes:

- 2 steps
- reduction required
- safety of NH_2OH
- high temperature reduction

Ti-mediated enamide synthesis with NH_3 (this work):

- 1 step
- redox neutral
- safe reagents
- room temperature

Scheme 1. Conventional two-step enamide synthesis and the direct Ti-mediated method.

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This reaction was first described in 1975 by Barton and co-workers. After a first step of oxime formation, the ketoxime was then treated with Ac_2O and either pyridine at reflux, $Cr(OAc)_2$, or $Ti(OAc)_3$ for reductive acylation.[13] Subsequently, numerous alternative reducing agents were developed.[14] The most commonly employed reductant is Fe powder, which was first demonstrated by Barton and Zard in 1985[14a] and subsequently developed by Burk and Zhang in 1998.[14b,c] From a large scale perspective, the use of high-energy hydroxylamine, generating a high-energy oxime intermediate, and reducing the oxime at high temperatures present safety concerns. In addition, the workup of the Fe process is often tedious, requiring filtration of large amounts of inorganic salts. While several alternatives to Fe metal have emerged recently, these still rely on the same overall two-step process through a ketoxime.[14d–g] Our own requirements for large-scale synthesis of *N*-acetyl enamides for asymmetric hydrogenation prompted us to develop a more direct and process-friendly alternative in which hydroxylamine is replaced with ammonia. Herein we describe a direct, redox-free synthesis of enamides from ketones, ammonia, and Ac_2O mediated by $Ti(OiPr)_4$. In addition, we introduce the use of edte (*N,N,N′,N′*-tetrakis(2-hydroxyethyl)ethylenediamine) to effect water solubilization of the Ti and allow a simple extractive workup.

Our strategy for enamide synthesis was based on condensation of a ketone with ammonia to give an *N*-unsubstituted imine or enamine, followed by *N*-acetylation on addition of Ac_2O. The imine formation presented a challenge due to the volatility of ammonia, which excluded the common method for imine formation by azeotropic distillation for removal of water.[15] Therefore the condensation with NH_3 at room temperature in the presence of various dehydrating agents was explored. Acetophenone **1** was treated with a dehydrating agent (2 equiv) and an ammonia source at room temperature for 24 h, followed by quenching with Et_3N and Ac_2O (Table 1). Little or no enamide **2** was observed with conventional desiccants and ammonia (entries 1–4). The use of sodium tetraborate ($Na_2B_4O_7$) or boric anhydride (B_2O_3) in THF or NMP gave modest conversion to product (entries 5–7). This prompted screening of other boron reagents, and the discovery that certain trialkyl borates, in combination with NH_4Br/Et_3N as the ammonia source, gave moderate conversions to product. The most effective boron reagent was 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (entry 11), which gave a 59 % conversion to **2**. The best results were obtained by using titanium alkoxides, however, with

Table 1: Screening results for direct enamide formation with NH₃.[a]

Entry	Dehydrant	NH₃ source	Solvent[b]	Conversion [%][c]
1	MgSO₄	NH₃/MeOH	THF	0
2	CaH₂	NH₃/MeOH	THF	8
3	ZnBr₂	NH₃/MeOH	THF	0
4	LiCl	NH₃/MeOH	THF	5
5	Na₂B₄O₇	NH₃/MeOH	THF	27
6	Na₂B₄O₇	NH₃/MeOH	NMP	40
7	B₂O₃	NH₃/MeOH	NMP	38
8	B(OMe)₃	NH₄Br/Et₃N	THF	<5
9	B(O*i*Pr)₃	NH₄Br/Et₃N	THF	34[d]
10	B(O*t*Bu)₃	NH₄Br/Et₃N	THF	<5
11	pinBO*i*Pr[f]	NH₄Br/Et₃N	THF	59[d]
12	Al(O*i*Pr)₃	NH₄Br/Et₃N	THF	32
13	Ti(OEt)₄	NH₃/MeOH	PhMe	85
14	Ti(O*i*Pr)₄	NH₃/MeOH	PhMe	96[e]
15	Ti(O*i*Pr)₄	NH₄Br/Et₃N	THF	67
16	Ti(O*t*Bu)₄	NH₃/MeOH	PhMe	22

[a] Typical reaction conditions: 2 equiv dehydrating agent, 2 equiv NH₃ source, 3 volumes of solvent, RT, 24 h, then 4 equiv Et₃N, 2 equiv Ac₂O. [b] THF = tetrahydrofuran, NMP = *N*-methylpyrrolidinone. [c] HPLC conversion of **1** to **2**. [d] After 48 h. [e] Yield of isolated product: 81%. [f] 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Ti(O*i*Pr)₄ being most effective (entry 14).[16] The use of ammonia in MeOH (1.5 equiv of 7 N solution) as the ammonia source and toluene as solvent was found to be optimal, and an 81% yield of isolated enamide **2** was obtained under these conditions after workup and chromatography. The use of ammonium salts in combination with Et₃N or other bases in place of 7 N NH₃ in MeOH led to lower reaction rates and lower yields.

While optimal reaction conditions which employed cheap, safe, and widely available reagents had been identified, the workup of the reaction required further optimization. Traditionally, reactions employing titanium alkoxides in combination with products which are not stable to aqueous acid are worked up by pouring the reaction mixture into brine or aqueous base.[16] This results in the precipitation of insoluble TiO₂ which is subsequently filtered, and the biphasic filtrate is worked up extractively. The filtration of TiO₂ is extremely slow, however, even on relatively small scales. This difficulty has been noted by others, and has unfortunately been the cause of abandonment of many Ti-based procedures for large scale applications.[17] When first scaling up the present reaction, the filtration required an unacceptable time (several hours to days) to complete, thus rendering the process impractical for large scale. Numerous variations of the aqueous solution used for quenching, order of addition, and filtration medium led to no improvement in filtration rate. We then investigated whether the Ti could be converted into a water-soluble species to avoid the filtration of TiO₂ altogether and allow an extractive workup. After screening several reagents, we found that edte effectively converted the Ti-(O*i*Pr)₄ into a water-soluble and water stable complex (Scheme 2).[18] The related reagent *N,N,N′,N′*-tetrakis(2-
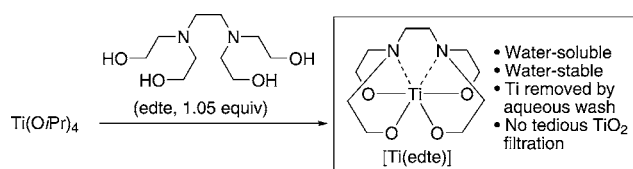
Scheme 2. Structure of edte and its complex with titanium.

hydroxypropyl)ethylenediamine (edtp) was equally effective, but more difficult to dispense than edte due to its greater viscosity. Importantly, both edte and edtp are inexpensive and commercially available in ton quantities.
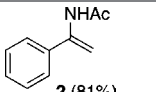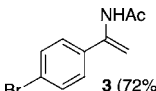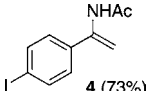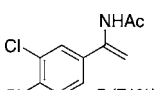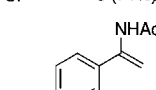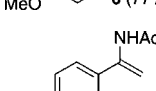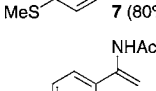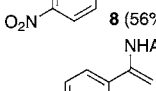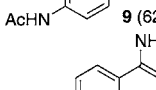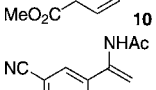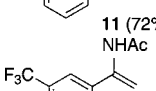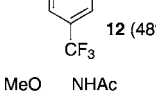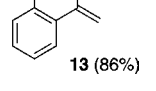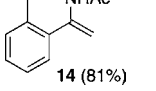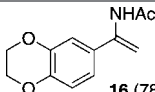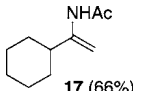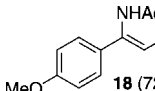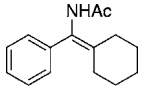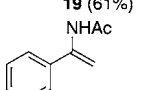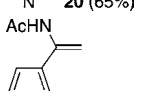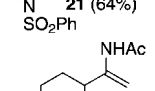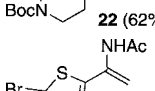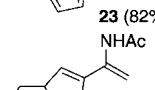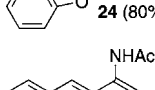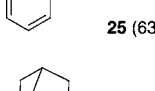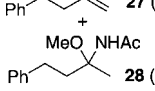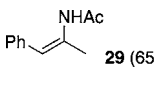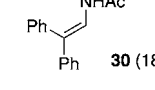
Thus, after completion of the reaction, 2.1 equiv of edte (1.05 equiv relative to Ti(O*i*Pr)₄) was charged, the reaction mixture heated at 55 °C for 15 min (to effect complete complexation of Ti with edte),[19] and after cooling to room temperature, the reaction mixture was diluted with aqueous NH₄OH and EtOAc.[20] This resulted in two clear phases, and allowed a normal extractive workup (Scheme 3). The use of edte should be applicable to the workup of other reactions employing stoichiometric titanium alkoxides, such as sulfinimine formation and reductive amination.[16]
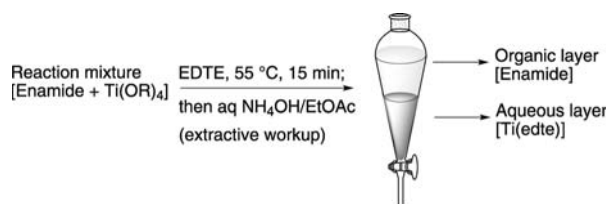
Scheme 3. Addition of edte to the reaction mixture enables simple extractive workup.

The scope of the enamide synthesis with acyclic ketones was explored (Table 2).[21] A variety of aryl methyl ketones were converted to the corresponding enamides in good yields. The reaction was tolerant of many functional groups, including halides, nitro groups, amides, esters, nitriles, and thioethers. The reaction with cyclohexyl methyl ketone (entry 16) and the related 4-piperidinyl methyl ketone (entry 21) proceeded to give exclusively the less substituted enamide, which may be difficult to achieve by alternative methods. The reaction was tolerant of α-branched ketones (entries 17, 18). Importantly, though the propiophenone substrate in entry 17 gave a mixture of *E*/*Z* isomers, it has been demonstrated that such mixtures are hydrogenated in high enantioselectivity.[1] In addition to aryl alkyl ketones, the reaction occurred equally well with heterocyclic ketones (entries 19–23). An enone provided a dienamide in good yield (entry 24). Benzylacetone reacted to give only the terminal enamide, but a significant amount of the methoxy aminal **28** was also formed in this case (entry 26). Phenylacetone gave exclusively the internal enamide with good selectivity favoring the *Z*-isomer (65% yield, *Z*:*E* = 5.5:1, entry 27)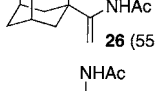. This result compares favorably with that obtained by the condensation of acetamide (24% yield, *Z*:*E* = 1.8:1).[7a] An aldehyde was converted in low yield to the corresponding enamide

Table 2: Scope of enamide formation with acyclic ketones.[a]

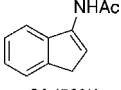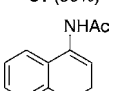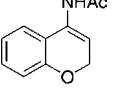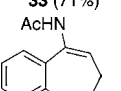| Entry	Enamide (yield)[b]	Entry	Enamide (yield)[b]
1	**2** (81%)	15	**16** (78%)
2	**3** (72%)	16	**17** (66%)
3	**4** (73%)	17	**18** (72%)[c]
4	**5** (71%)	18	**19** (61%)
5	**6** (77%)	19	**20** (65%)
6	**7** (80%)	20	**21** (64%)
7	**8** (56%)	21	**22** (62%)
8	**9** (62%)	22	**23** (82%)
9	**10** (81%)	23	**24** (80%)
10	**11** (72%)	24	**25** (63%)
11	**12** (48%)	25	**26** (55%)
12	**13** (86%)	26	**27** (51%) + **28** (28%)
13	**14** (81%)	27	**29** (65%)[d]
14	**15** (84%)	28	**30** (18%)

[a] Reaction conditions: 10 mmol ketone, 15 mmol NH₃/MeOH, 20 mmol Ti(O*i*Pr)₄, 6 mL PhMe, RT, 24 h; 40 mmol Et₃N, 20 mmol Ac₂O, RT, 1–3 h. [b] Yield of isolated products. [c] 2:1 mixture of *Z:E* isomers. [d] 5.5:1 mixture of *Z:E* isomers.

(entry 28). The enamide formation was also amenable to cyclic ketone substrates (Table 3). Indanone, tetralone, chromanone, and suberone substrates all provided the corresponding enamides in good yields.

Table 3: Scope of enamide formation with cyclic ketones.[a]

Entry	Enamide (yield)[b]	Entry	Enamide (yield)[b]
1	**31** (50%)	3	**33** (71%)
2	**32** (85%)	4	**34** (76%)

[a] Reaction conditions: 10 mmol ketone, 15 mmol NH₃/MeOH, 20 mmol Ti(O*i*Pr)₄, 6 mL PhMe, RT, 24 h; 40 mmol Et₃N, 20 mmol Ac₂O, RT, 1–3 h. [b] Yield of isolated products.

The intermediate formed from the reaction of ketones with amines in the presence of Ti(O*i*Pr)₄ has been postulated as an *O*-titanium hemiaminal by several groups, although no direct spectroscopic evidence has been provided.[16a,c,22] On the other hand, in the context of their work on reductive amination, Brunel and co-workers studied the species formed from acetophenone, benzylamine and Ti(O*i*Pr)₄ by ¹H and ¹³C NMR spectroscopy and reported no evidence of an *O*-titanium hemiaminal but suggested the intermediacy of acetophenone *N*-benzyl imine.[23] In order to gain insight into the intermediate generated in the present reaction, we performed IR and NMR experiments (Scheme 4). Thus, acetophenone **1** was treated with methanolic ammonia and Ti(O*i*Pr)₄ in C₆D₆, and the reaction solution was allowed to stir for 20 h at room temperature. IR analysis of the reaction showed the disappearance of the acetophenone carbonyl at 1692 cm⁻¹ concurrent with the appearance of a new peak at 1626 cm⁻¹, a frequency typical of an aryl ketimine C=N bond.[24] Analysis of the ¹³C NMR spectrum showed the disappearance of the acetophenone carbonyl signal at 197 ppm and the appearance of a new peak at 175 ppm, also a frequency consistent with a ketimine species.[24] The ¹³C HMBC spectrum showed strong correlations between the carbon signal at 175 ppm and the two *ortho* protons at 7.51 ppm as well as the methyl protons of the acetophenone moiety at 2.07 ppm. These correlations confirmed the identity of the 175 ppm signal as the former carbonyl carbon. The ¹⁵N

IR: 1626 cm⁻¹
¹³C NMR: 175 ppm (C=N)
¹⁵N NMR: 89 ppm
¹⁵N HSQC: no proton bonded to nitrogen
a: ¹³C HMBC correlations
b: ¹⁵N HMBC correlation

35 (R = *i*Pr or Me)
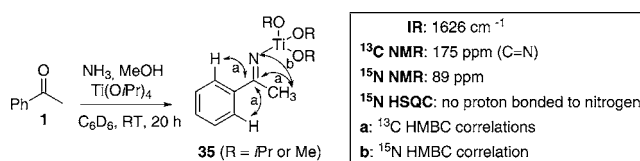
Scheme 4. Spectral data for proposed imine intermediate **35**.

HMBC spectrum showed a strong correlation between the methyl protons at 2.07 ppm and a nitrogen signal at 89 ppm. The ^{15}N HMBC data, together with the ^{13}C HMBC data, suggest the formation of an imine species. Furthermore, the ^{15}N HSQC spectrum showed no evidence of an N-H correlation with the nitrogen resonance at 89 ppm. In addition the ^1H NOESY spectrum revealed correlations between the aromatic protons at 7.15 and 7.51 ppm and the methyl protons on the titanium isopropoxide moiety at 1.09 ppm establishing a proximity of < 5 Å. Based on these spectral data, we postulate that the imine nitrogen is covalently bound to titanium as shown by **35** in Scheme 4.[25] The nature of the titanium center is more difficult to specify, as methanol may be exchanging with the isopropoxy ligands on the metal, and the imine-titanium complex may be dinuclear.[26]

In order to further corroborate structure **35**, we attempted to prepare it from an alternate route (Scheme 5). Thus, acetophenone imine was synthesized by the addition of MeLi to benzonitrile **36** and quenching with MeOH, followed by
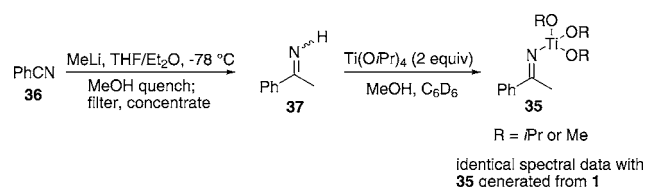
Scheme 5. Independent generation of **35** from acetophenone imine **37**.

filtration and concentration.[15b] Imine **37** was cleanly formed as a 2.1:1 mixture of NH isomers. Treatment of a C_6D_6 solution of **37** with 2 equiv of Ti(OiPr)$_4$ and aging for 18 h gave a species which by ^1H and ^{13}C NMR contained very broad signals, suggesting the formation of a paramagnetic complex. On addition of MeOH (a volume equal to that present in the reaction from the 7 N NH$_3$/MeOH solution) and aging for 30 min, the ^1H and ^{13}C NMR spectra showed formation of a species identical with **35** by ^1H and ^{13}C NMR. We speculate that MeOH may facilitate the incorporation of imine **37** as a covalent ligand on titanium by exchanging with one or more of the isopropoxy groups and thereby reducing steric crowding on the titanium center. It is clear from this experiment that MeOH plays a critical role in allowing complex **35** to form. The preparation of **35** from imine **37** offers further support for the proposed structure.

Based on these data, the mechanism of the reaction can be postulated as shown in Scheme 6. The reaction of methanolic ammonia with acetophenone in the presence of Ti(OiPr)$_4$ generates an imine species such as **35**. The spectral data do not support the formation of a hemiaminal intermediate such as **38**. On addition of Et$_3$N and Ac$_2$O, imine **35** is acetylated to give **39**, which subsequently isomerizes to the product enamide **2**.[27]

In summary, we have developed a practical, safe and economical one-step synthesis of enamides from ketones using Ti(OiPr)$_4$, ammonia, and acetic anhydride. The reaction occurs under mild conditions and shows excellent functional-
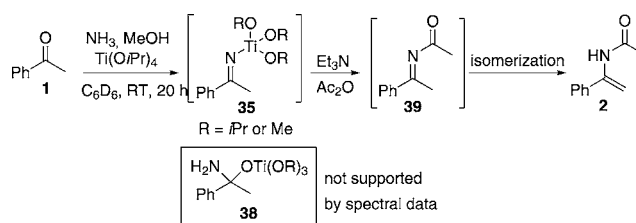
Scheme 6. Proposed mechanism of enamide formation.

group tolerance. This process avoids the safety concerns of the hitherto commonly employed two-step ketoxime reductive acylation process, namely the use of high-energy hydroxylamine and oxime intermediates. The process requires no reduction, and therefore avoids the need for large quantities of Fe powder and the associated post-reaction filtration of Fe salts. Spectroscopic analysis of the reaction mixture confirmed the formation of an imine and not a hemiaminal intermediate prior to acetylation. To overcome the difficult filtration of TiO$_2$ encountered in a traditional aqueous quench, the use of edte to generate a water-soluble and water-stable titanium complex was employed. This enables a simple extractive workup amenable to large scale synthesis. The use of edte in the workup of reactions using titanium alkoxides should be of general utility to both academic and industrial chemists.

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