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Synthesis of sterically hindered enamides *via* a Ti-mediated condensation of amides with aldehydes and ketones†

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The first $TiCl_4$-mediated condensation of secondary amides with aldehydes and ketones has been achieved. The reaction proceeds at room temperature and is complete within 5 h in most cases. The optimized procedure used 5 equiv of an amine base hinting that the *in situ* activation of both the amide and the Lewis acid is required. The reaction affords polysubstituted (*E*)-enamides.

Enamides[1] are an emerging class of substrates for the synthesis of chiral amines *via* asymmetric hydrogenation[2] and more importantly for the synthesis of saturated and unsaturated heterocycles.[3] Considering the extensive patent coverage of heterocyclic moieties in the pharmaceutical industry, access to new heterocycles or those with unusual substitution patterns is increasingly needed.[4] From a synthetic viewpoint, a variety of reaction strategies to synthesize enamides have been disclosed in the literature.[5] The most widely applicable routes to enamides remain the Cu- and Pd-catalyzed processes developed by Buchwald,[5o] Porco,[5p] Ma[5q] and others[5k–q] and more recently refined by Batey.[5k] With the exception of Batey's procedure, which still uses excess amount of the precious organotrifluoroborate salts (2–5 equiv.), these transition metal catalyzed reactions require high temperature, very strong bases, and careful exclusion of air. It should be noted that these methods are not applicable to the synthesis of hindered enamides due to the limited supply of complex vinyl halides/borates and/or the difficulty to synthesize them. Recently, a two-step procedure based on the Heck arylation of preformed enamides was introduced as a potential solution to this problem, although only β-amidoacrylates were extensively investigated.[5n] Overall, the synthesis of sterically congested enamides still represents an unsolved synthetic problem.

There has been a long standing interest in converting carbonyl compounds into enamides.[3h,6] The most widely used procedures uses *p*-TsOH in refluxing toluene over a long period of time (1–5 days).[6a] Broadly speaking, hindered substrates do not work well under these conditions.[3h] More recently, a chemical development group at Boehringer Ingelheim[6d] has successfully converted ketones into *N*-acetyl enamides using ammonia and acetic anhydride at room temperature. The use of other amines or anhydrides in this reaction has not been reported. The conversion of carbonyl compounds to enamides is advantageous due to their long shelf life, low cost and ease of access. Herein, we present a new route to polysubstituted enamides that uses readily available amides and carbonyl compounds. The reaction proceeds at room temperature (and even below), and is complete mostly within 5 h.

A preliminary screening was carried out using 2-pyrrolidinone and cyclohexanecarboxaldehyde (entry 1, Table 1). We aimed at identifying conditions that would promote this very sterically demanding condensation reaction at a mild temperature. The use of a strong Lewis acid was thought to be essential in order to overcome the low inherent nucleophilicity associated with amides by analogy to the use of *p*-TSA under the previously mentioned condition.[6a] $BF_3{\cdot}OEt_2$, $Zn(OTf)_2$, $AlCl_3$, $MgCl_2$, $Ti(Oi\text{-}Pr)_4$ and $TiCl_4$ all failed to promote the desired reaction. We reasoned that a base may be required to activate the amide, and/or facilitate the tautomerization of the transiently formed *N*-acyl iminium intermediate. When NEt_3 was combined to the above Lewis acids, again no reaction was observed with $BF_3{\cdot}OEt_2$ and $Zn(OTf)_2$ while $AlCl_3$, $MgCl_2$, and $Ti(Oi\text{-}Pr)_4$ only afforded varying amount of *N*-acyl hemiaminal intermediate (see supporting information). Gratifyingly, $TiCl_4$ enabled the formation of the desired enamide **1** in very good isolated yield (73%). To the best of our knowledge this is the first time that a Lewis acid has been used to make enamides from amide nucleophiles at room temperature. We next turned our attention to the nature of the base, which proved more critical than expected. DIPEA, DBU, and Cs_2CO_3 all appeared inferior in yields while DABCO, *t*-BuONa, and NaOH did not promote any reaction (see supporting information). Further optimization revealed that the amount of NEt_3 (*i.e.* 5 equiv. as opposed to 1, 2.5, and 10 equiv.) was crucial to achieve a good yielding transformation. This preliminary screening informed our choice to use the $TiCl_4/Et_3N$ combination. Ti-complexes with an amine base are known to promote a range of synthetic transformations, oftentimes tolerating the presence of very sensitive substrates.[7]

Next, we explored the substrate scope of this new transformation (Table 1). 2-Pyrrolidinone was reacted with a range of aldehydes of different steric hinderance starting with cyclopentane- and cyclooctane-carboxaldehydes. In both cases the desired products were obtained in moderate to good yield (49 and 62% respectively, entry 1). To probe the steric effect in acyclic series, we started our

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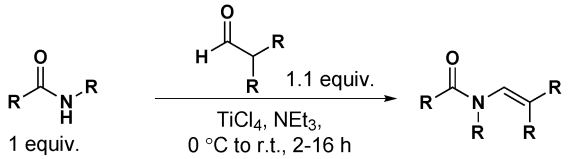
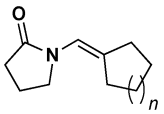
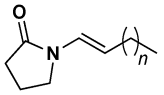
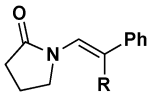
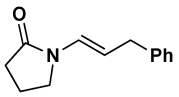
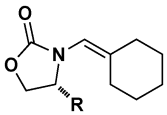
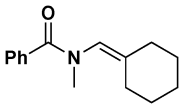
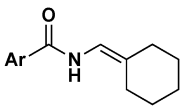
Table 1 Ti-mediated condensation of amides with aldehydes



Entry	Enamide product		Yield[a] (%)
1		**1**: n = 1, **2**: n = 0, **3**: n = 3	73,15[c] 49[b] 62
2		**4**: n = 3	54[c] *E only* 30
3		**5**: R = H **6**: R = Me	46 *E only* 15[c] 43 *Z*:*E* 30[c] 1:1.3
4		**7**	35 *E only*
5		**8**: R = H **9**: R = Ph	54 14[c] 54
6		**10**	75[b,d]
7		**11**, Ar = Ph, **12**, Ar = (*p*-CF_3)Ph, **13**, Ar = (*o*-Me)Ph,	20[b] 17[b] 8[e]

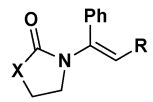
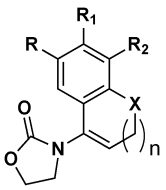
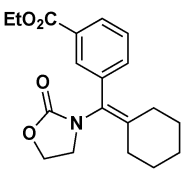
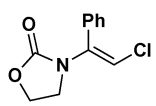
[a] Standard condition: $TiCl_4$ (1.2 equiv.), NEt_3 (5 equiv.), 0 °C to r.t., DC., 2–16 h. [b] NMR yield. [c] Using DBU. [d] 75% at 60 °C in DCE. Heating did not prove beneficial for other substrates. [e] NMR yield only, not purified.

investigation with a simple heptanal system. To our surprise, the yield of the reaction was very low (30%, entry 2). However the yield of the reaction nearly doubled when DBU was used as a base in lieu of Et_3N firmly establishing the strong dependence of this reaction on the nature/strength of the base. When 2-phenyl acetaldedyde was used as substrate, the desired product was isolated in 46% yield (entry 3) under the standard reaction conditions against 15% for the DBU protocol. A similar trend was observed with 2-phenyl propanal (entry 4). Taken together, these results suggest that a small base should be used when condensing hindered substrates, whereas a strong base is preferred for unhindered aldehydes. In addition, erosion of stereoselectivity was observed when a branched aldehyde was used (1.3 : 1 *E*, *Z* ratio, entry 3). The reaction is also compatible with the use of carbamates affording the oxazolidinone adduct **8** in moderate yield (entry 5). Remarkably, 4–phenyloxazolidinone performed equally well in this union between two highly hindered substrates (entry 5, 54%). Acyclic secondary amide *N*-methyl benzamide also afforded the corresponding enamide **10** in very good yield (75% at 60 °C in DCE, 46% at rt, entry 6). Primary amides proved equally reactive although the corresponding products were isolated in low yield due primarily to stability issues (entry 7).

To explore the access to even more complex enamides, we investigated the applicability of this methodology to ketone substrates (Table 2). Without any optimization, we were pleased that 2-pyrrolidinone could be condensed with an unsymmetrical ketone to form α,β-disubstituted enamide **14** in good yield and very high stereoselectivity (entry 1). Interestingly, no loss of reactivity was observed in the formation of enamide **14** compared to the condensation with the less hindered phenylacetaldehyde (51% *vs.* 46% yield – Table 2, entry 1 *vs.* table 1, entry 3).

As observed for the coupling with aldehydes, moving from 2-pyrrolidinone to an oxazolidinone coupling partner did not influence the yield or the stereoselectivity of the reaction (14 *vs.* 15, entry 1, Table 2). Noteworthy, enamide **15** was obtained (*E*)-stereoselectively as opposed to Park's protocol[5n] that affords the complementary (*Z*)-isomer. Acetophenone also proved to be a good substrate to afford the geminal bis-substituted enamide **16** (80% NMR yield, 52% isolated). Cyclic ketones were also investigated. Simple dihydronaphthalen-1-yl oxazolidinones were previously prepared in very good yield *via* an arene-ynamide cyclization protocol,[8] wherein the precursor must be prepared *via* a multi-step sequence. Here, we can access a more complex derivative in one step from commercially

Table 2 Ti-mediated condensation of amides with ketones

Entry	Enamide product		NMR yield/isolated yield (%)
1			
	X = C, R = Ph	**14**	51/nd *E only*
	X = O, R = Ph	**15**	50/(45) *E only*[a]
	X = O, R = H	**16**	80/52
2			
	n = 1, X = C, R, R_2 = H, R_1 = Br	**17**	54/43
	n = 1, X = O, R, R_1 = H, R_2 = Br	**18**	54/49
	n = 0, X = C, R = F, R_1, R_2 = H	**19**	46/38
3		**20**	32/19
4		**21**	18/11 *E only*[a]

[a] The olefin geometry of **14** confirmed by nOe, geometry of **15** and **21** were assigned by analogy to **14**; nd = not determined.

available starting materials. For instance, oxazolidinone reacted with halogenated dihydronaphtalenone to afford **17** in 43% isolated yield (entry 2). The presence of an ether functionality is also compatible with our reaction conditions (entry 2) as well as the use of indanone derivatives (entry 2). Finally, we attempted to access unprecedented tetrasubstituted and halogenated enamides. In both cases, desired products **20** and **21** could be isolated without any optimization albeit in low yield (entries 3 and 4).

While the detailed mechanistic picture of this reaction remains unclear, several lines of evidence point to a mechanism distinct from the classic *p*-TSA catalyzed enamide synthesis reactions. First, the reaction does not proceed in the absence of an organic base. Second, weaker Lewis acids only afforded *N*-hemiaminal intermediates in the presence of the base. Third, the reaction showed a strong dependence on the nature/strength of the base; for unhindered carbonyl substrates the yield of the reaction increases with the use of stronger bases whereas for hindered carbonyl compounds steric considerations prevailed. Taken together, these observations paint a mechanistic picture that is consistent with a tandem aza-aldol/*E2*-elimination mechanism. Finally, the optimal reaction conditions required the use of 5 equiv of the base. Under this scenario, the displacement of the chloride by excess base to generate a Ti-NEt_3 adduct, an even stronger Lewis acid, is plausible.[9] Indeed, the activation of Lewis acids by Lewis bases is a known concept that has been well described in the literature especially for weak Lewis acids such as $SbCl_4$, $SiCl_4$, or Se derivatives.[10] The metal center in the resulting adduct is thought to be more electropositive than without base. By analogy and even though such activation does not seem to be reported for Ti(IV) complexes, it appeared plausible to us to think that the strong inherent acidity of $TiCl_4$ may generally hide its activation by Lewis bases, and thus be less visible than for weak acids (*e.g.* $SiCl_4$). This Lewis base activation would only become beneficial for reactions of high activation energy where $TiCl_4$ alone is not sufficient to promote the transformation.

We have developed a convenient condensation of secondary amides with a variety of carbonyl compounds in one step at room temperature using the unique combination of $TiCl_4$ and NEt_3 to generate polysubstituted enamides in moderate to good yields. We expect the new enamides synthesized herein to find application in asymmetric hydrogenations,[2] and the synthesis of diverse heterocyclic cores.[3]

Novartis Office of Education, Diversity, and Inclusion and Patience Moyo are acknowledged.

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