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Org. Process Res. Dev., **Just Accepted Manuscript** • Publication Date (Web): 21 Feb 2017

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Stereochemical Aspects of T3P Amidations

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Submitted February 3, 2017

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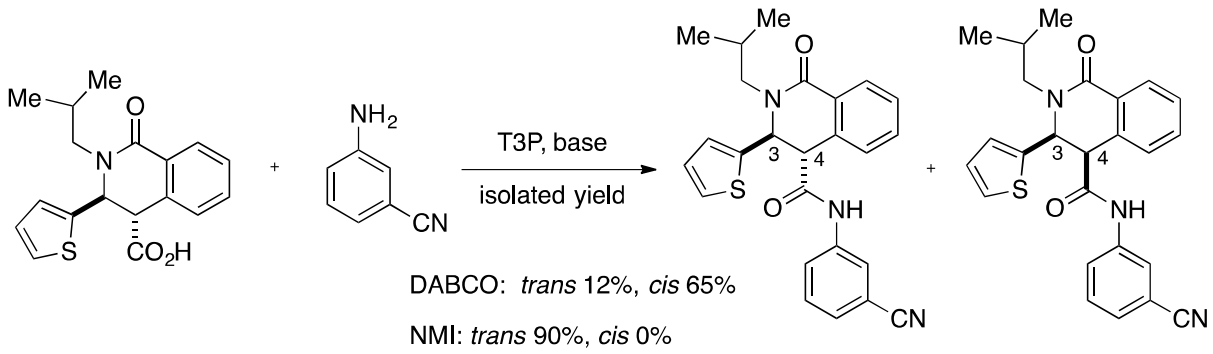


Abstract

Propanephosphonic acid anhydride (T3P) is a process friendly commercial reagent that is useful for direct carboxamide formation from the carboxylic acid and amine components. For amidation reactions of certain tetrahydroisoquinolonic carboxylic acids and electron-poor anilines, the phosphonate carboxylate mixed anhydride intermediate evidently eliminates under the basic conditions to give a ketene, whose addition reaction in turn leads to a mixture of diastereomeric amide products. For example, 1,4-diazabicyclo[2,2,2]octane (DABCO), used as the base, provides mostly the 3,4-*cis* product, whereas *N*-methylimidazole (NMI) leads efficiently to the 3,4-*trans* product. A mechanistic rationale, along with compelling evidence for the intermediate ketene, is provided, as well as several examples of the efficient T3P-mediated preparation of carboxamides that are of interest as active anti-malarials.

Key Words

Ketene dimerization

Allene

Infrared

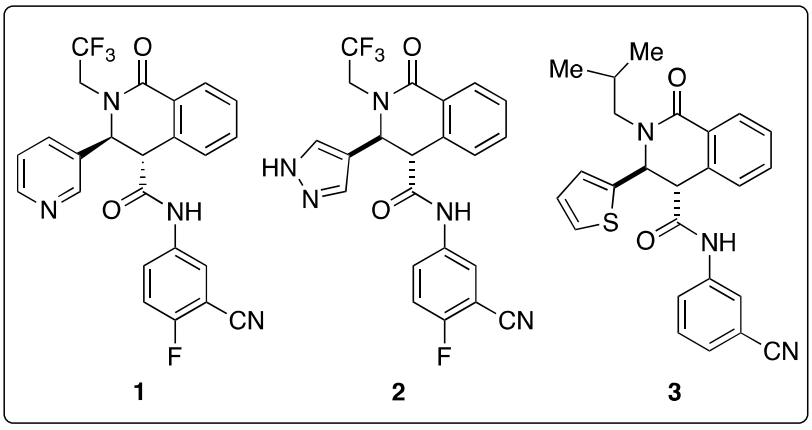
Epimerization

Phosphoryl chloride

Crystallography

Introduction

Malaria infects many millions and kills hundreds of thousands of people each year, despite the wide success of drug regimens, indoor spraying, and treated mosquito nets.[1,2] Combination therapies based on the artemisinin class of anti-malarials, once the best such weapons against the disease, are beginning to encounter resistance among *Plasmodium* species, necessitating the continual development of new drug candidates with new modes of action.[3] As the result of an extensive program of phenotypic screening, and subsequent hit-to-lead developmental studies, the tetrahydroisoquinoloic carboxanilide SJ733, a *Pf*ATP4 inhibitor, was recently identified as candidate for clinical studies against malaria infection.[4,5,6,7] The chemical synthesis of SJ733 and its analogues depends on the reaction of homophthalic anhydride with an *N*-substituted heteroarylcarboximine,[8,9] followed by an amidation with the appropriately substituted aniline. The free base form of SJ733 is shown below as **1**. The development of efficient and practical amidation reactions to prepare **1** as well as several other active analogues, including **2** and **3**, from the corresponding carboxylic acids is the subject of this report.



Results and discussion

Amidation is one of the most important reactions in medicinal chemistry. A wide variety of reagents and methods for amidation of carboxylic acids and amines, including relatively electron-poor anilines, are available,[10] and many of these are suitable for large-scale synthesis.[11] We initially investigated the use of phosphoryl chloride[12] ($POCl_3$), an inexpensive reagent that has been used for kilogram scale reactions,[13] and, despite the toxicity[14] and workup risks,[15] has among its advantages the potential for developing a simple one-pot operation.

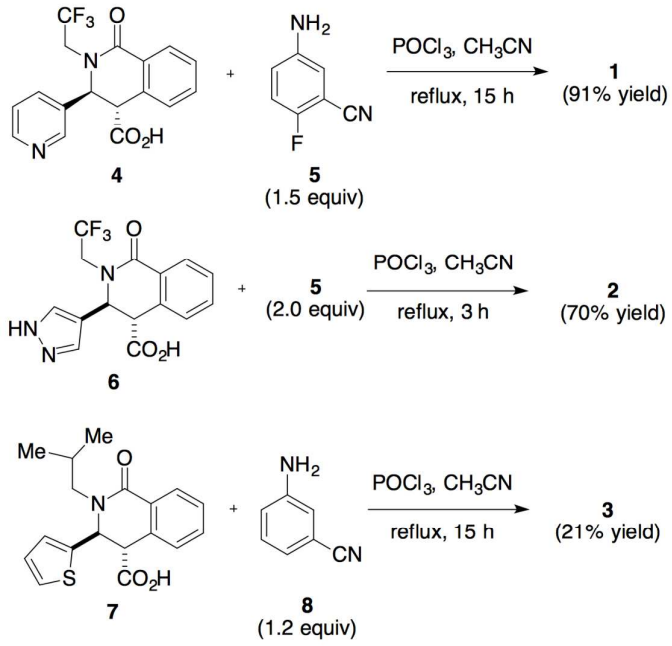
Thus, treatment of the resolved tetrahydroisoquinolonic 4-carboxylic acid,[9] **4**, with 5-amino-2-fluoro-benzonitrile (**5**) and $POCl_3$ in acetonitrile solution at reflux led to the efficient production of the desired carboxanilide **1** (Scheme 1) on a multi-gram scale. No base is required – the reaction probably proceeds by way of the acid chloride of **4**; protonation of the aniline **5** (pK_a of the conjugate acid ~ 2)[16] by

the hydrochloric acid produced during this initial process can be tempered by the basic pyridine nitrogen (pK_a ~ 5) of the substrate itself.

Similarly, the reaction of **5** with the pyrazol-4-yl analogue, racemic carboxylic acid,[9] **6**, gave its carboxanilide **2** on gram scale, albeit in somewhat lower yield. The pyrazolyl ring of **6** (pK_a ~ 3)[17] is less basic than pyrid-3-yl, and additionally offers a potentially interfering nucleophilic site (N-2),[18] so a less efficient amidation might be rationalized.

The $POCl_3$ method collapsed dramatically when applied to the case of racemic 3-(thien-2-yl) acid[9] **7** and the coupling partner 3-aminobenzonitrile (**8**); the reaction provided carboxanilide **3** in poor yield. Because we required a variety of analogues similar to **3**, the development of a more generally applicable amidation method for tetrahydroisoquinolonic carboxylates warranted some additional work. We examined the coupling reagent *n*-propanephosphonic acid anhydride (T3P), commercially available as a 50% solution in ethyl acetate, and a highly touted promoter[19,20] for kilogram-scale amidation of racemization-prone carboxylic acid substrates.

Scheme 1. Amidations with Phosphoryl Chloride

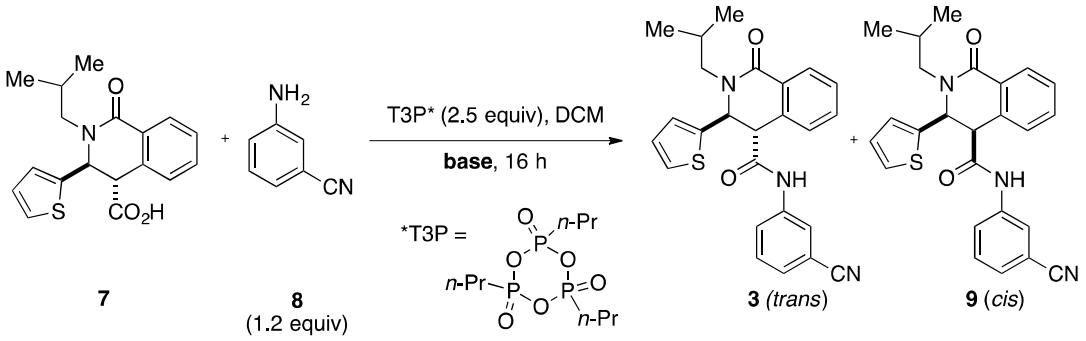


The initial attempt to couple carboxylate **7** with aniline **8** under conventional T3P conditions,[19] namely, the use of 2 equiv of triethylamine as base in dichloromethane / ethyl acetate solution at room temperature, led to partial conversion to, and a disappointingly low isolated yield of, amide **3** (entry 1, Table 1). An increase in the amount of triethylamine (entry 2) gave more of amide product, but now **3** was accompanied by a significant portion of its 3,4-*cis* isomer, **9**. Further increases in the amount of

triethylamine led to a corresponding increase in the amount of isolated *cis* product relative to *trans* (entries 3 and 4), up to a 4.3:1 ratio. The addition of 0.2 equiv of the acyl transfer promoter 4-(N,N-dimethylamino)pyridine (DMAP, entry 5) to the triethylamine reaction improved the overall yield (compare entry 1), but nevertheless led to significant amounts of *cis* amide product. The reactions in Table 1 were started at 0 °C and allowed to stir at room temperature overnight; chromatography on silica employed hexane/ethyl acetate mixtures as eluant.

Additional bases were screened (Table 1), including the less-hindered *N*-methylpyrrolidine (NMP, entry 6), the less-basic *N*-methylmorpholine (NMM, entry 10), the less-hindered and less-basic 1,4-diazo[2.2.2]octane (DABCO, entry 9), and the acyl-transfer promoters pyridine (entries 7 and 8) and *N*-methylimidazole (NMI, entries 11–16). The latter two bases gave the best yields of (*trans*) **3**, without any accompanying *cis* isomer. A Pfizer group successfully employed pyridine as a base for T3P amidations of amino acids to minimize racemization.[20] The same group noted that addition of DMAP led to increased racemization. DABCO, used in excess (4 equiv), gave the highest isolated yield and ratio of *cis* to *trans* product (respectively 67% and 5.6:1, entry 9). The best yield of (*trans*) **3**, 91%, was obtained with 2 equiv of NMI (entry 12). Reducing the amount of T3P (entry 13), increasing the amount of NMI (entries 14 and 15) or switching the solvent to ethyl acetate (entry 16), did not improve the yield.

Table 1. T3P Amidations – Base Optimization



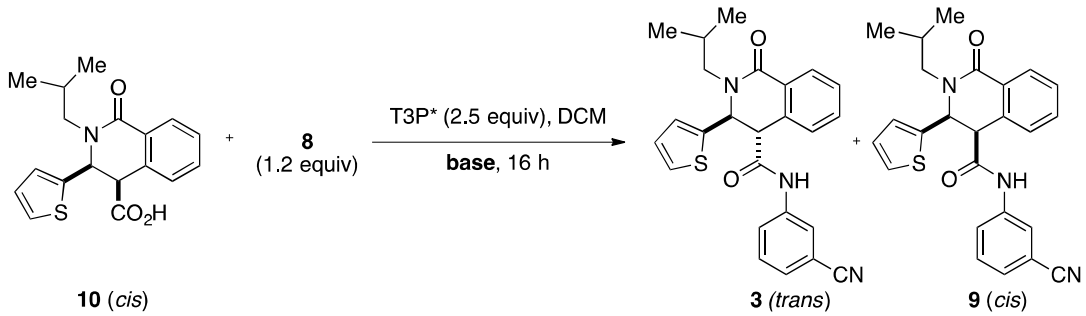
Entry	Base (pK_a)[a]	Equiv	Yield (**3**)[b]	Yield (**9**)[b]	Notes
1	Et_3N (10.7)	2	31%	0%	**7** (25%)[c]
2	"	4	31%	23%	**7** (15%)[c]
3	"	7	12%	54%	
4	"	14	15%	65%	
5	"	2	58%[d]	18%[d]	0.2 equiv DMAP[e]
6	NMP[f] (10.3)	2	43%	23%	
7	pyridine (5.2)	1	63%	0%	
8	"	2	87%	0%	
9	**DABCO[g] (8.8)**	**4**	**12%**	**67%**	
10	NMM[h] (7.4)	4	80%	5%	
11	NMI[i] (7.0)	1	25%	0%	

12	"	**2**	**91%**	**0%**	
13	"	2	87%	0%	1.5 equiv T3P
14	"	4	80%	0%	
15	"	8	77%	0%	
16	"	2	75%	0%	in ethyl acetate

[a] approximate pK_a of the conjugate acid
[b] isolated yield from column chromatography unless otherwise indicated
[c] recovered starting material
[d] NMR yield vs internal standard
[e] DMAP = 4-(N,N-dimethylamino)pyridine
[f] NMP = *N*-methylpyrrolidine
[g] DABCO = 1,4-diazabicyclo[2.2.2]octane
[h] NMM = *N*-methylmorpholine
[i] NMI = *N*-methylimidazole

For comparison, T3P promoted amidations of the *cis* carboxylate **10** were also examined (Table 2). The starting material **10** is available by a modification of the HPA/imine cycloaddition that affords **7** (see Experimental Section). Reaction of **10** under the best conditions for making **9** from **7**, namely 4 equiv of DABCO in dichloromethane solution, gave the same products (**3** and **9**) in virtually identical yields and ratio (entry 1). However, the best conditions for making **3** from **7** (namely, 2 equiv of NMI), led to an almost equal mix of **3** and **9** (entry 3). How can the formation and ratios of **3** and **9** be rationalized?

Table 2. T3P Amidations – *Cis* Carboxylate Starting Material



10 (*cis*) **3** (*trans*) **9** (*cis*)

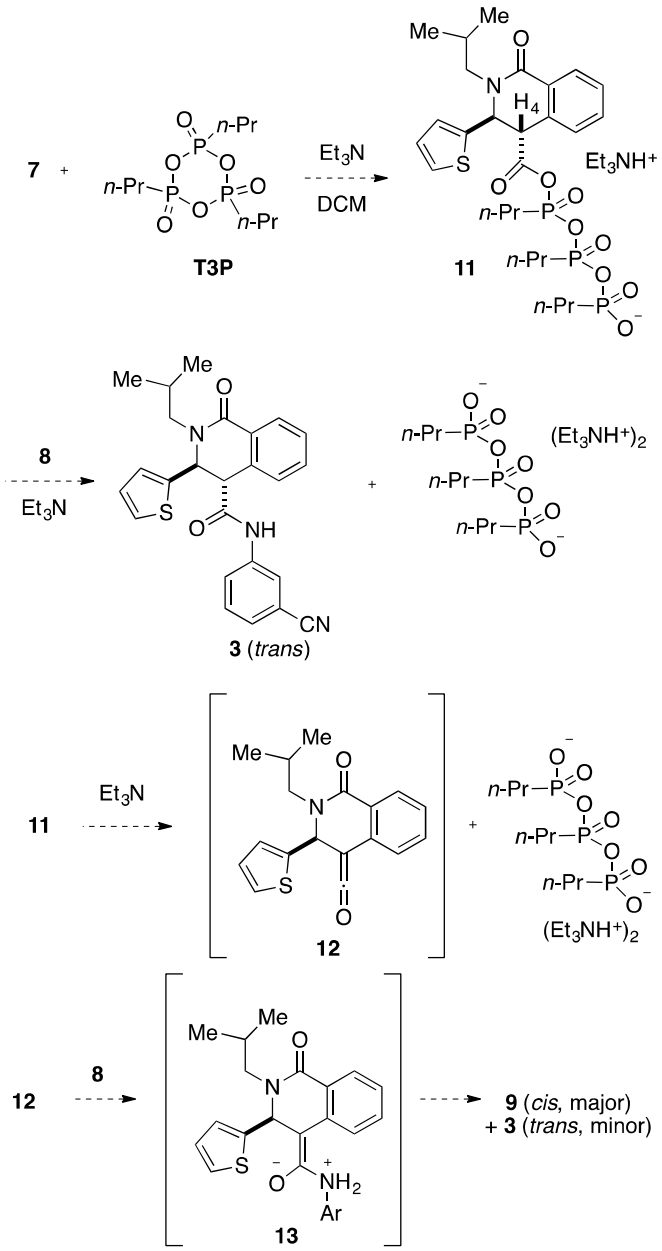
Entry	Base (pK_a)[a]	Equiv	Yield (**3**)[b]	Yield (**9**)[b]	Compare yields from **7** (*trans*)
1	DABCO[c] (8.8)	4	12%	65%	**3** (12%) and **9** (67%)
2	Et_3N	4	10%	66%	**3** (31%) and **9** (23%)
3	NMI[d] (7.0)	2	49%	44%	**3** (91%) and **9** (0%)

[a] approximate pK_a of the conjugate acid
[b] isolated yield from column chromatography
[c] DABCO = 1,4-diazabicyclo[2.2.2]octane
[d] NMI = *N*-methylimidazole

The triethylamine-promoted formation of varying amounts of *cis* product **9** from *trans* acid **7** during T3P amidation can be understood by the following the mechanistic steps proposed in Scheme 2. Normally, the T3P mediated formation of amide is thought to proceed by way of the carboxylate tris(phophonate) mixed anhydride **11**. Displacement of the tris(phosphonate) leaving group by aniline **8** leads directly to the *trans* carboxanilide **3**.

Alternatively, triethylamine can promote removal of the proton at H-4, accompanied or followed by vicinal loss of the tris(phosphonate) dianion, to provide ketene **12**. Addition of the aniline to **12** would give an intermediate, **13**,[21] that could protonate at C-4 kinetically and preferentially from the face opposite to the bulky thienyl substituent, leading mostly to *cis* product **9**. The two sets of reaction conditions that might be deemed most likely to favor base-promoted elimination (excess triethylamine, Table 1, entry 4; and the somewhat less basic but much less hindered DABCO, Table 1, entry 8), do indeed lead to similar product mixtures favoring **9**. Furthermore, DABCO gives the same product mixture starting from either the *cis* or *trans* acid. These observations can be taken as strong circumstantial evidence for formation of ketene intermediate **12**. The facial preference for protonation of **13** appears to be as much as 5.6:1 (*cis*/*trans* for the the DABCO reaction of **7**; triethylamine in excess gives 4.3:1). Ratios smaller than 5.6:1 (not as much *cis*) would then reflect the extent of direct displacement reaction of **11**. It should be noted that the 2,3,4-trisubstituted tetrahydro-2-isoquinolone systems, exemplified by both carboxamides and carboxylic acids (**1**, **2**, **3**, **4**, **6**, and **7**), exhibit a complete preference for the *trans* isomers at equilibrium, and these would not at all be expected to isomerize to detectable amounts of *cis* under conditions of reversible deprotonation at C-4.

Scheme 2. Ketene Formation Proposed During T3P Amidation



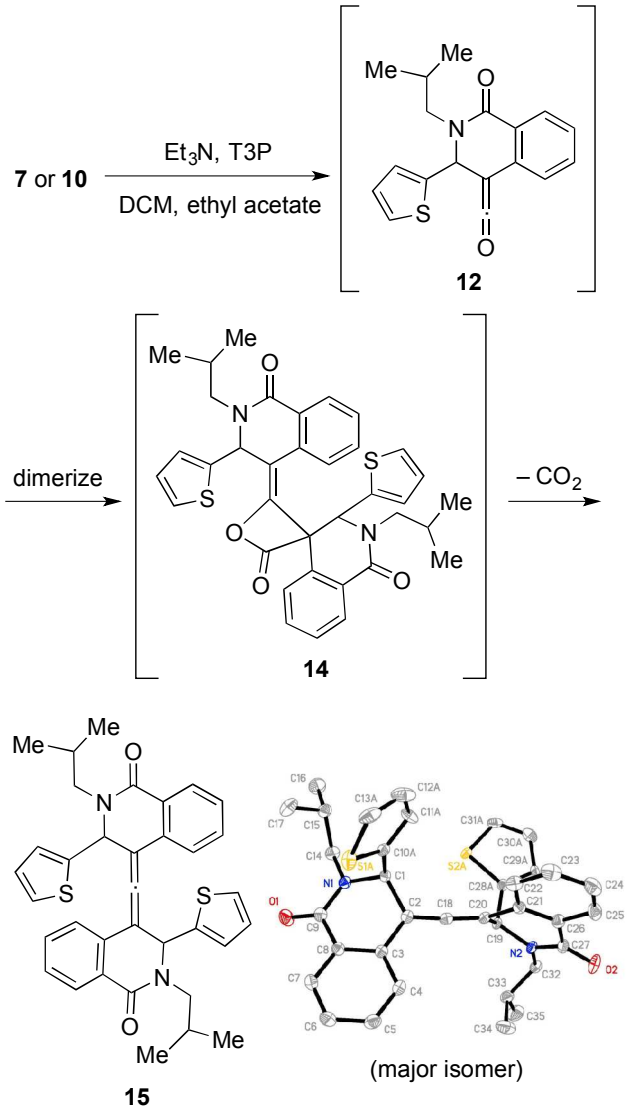
The reaction of simple carboxylic acids with T3P under conditions similar to those described here has been used to make ketenes that were trapped *in situ* by imines to complete a Staudinger 2-azetidinone synthesis.[22,23,24] In these cases, the intermediate mixed triphosphonate anhydride (compare **11**) likely undergoes a base promoted vicinal elimination process. Compelling evidence for the formation of ketene **12** during the amidations of tetrahydroisoquinolonic carboxylates was obtained by individually treating the *trans* and *cis* acids (**7** and **10**, respectively) with triethylamine and T3P as before (Table 1), but in the absence of the aniline nucleophile (Scheme 3). Infrared spectroscopic analysis of crude reaction mixtures in

each case (spectra taken over the reaction time period of 1 to 10 min) showed the diagnostic absorbance for the presence of ketene at 2119 cm^{-1}. This signal faded after 10 min.

From each reaction, allenes **15** were chromatographically isolated as an identical 26:5:4 mixture of all three possible diastereomers (28% and 60% respective combined yields from **7** and **10**), and these were characterized by their H-1 NMR, C-13 NMR, infrared (diagnostic λ_{max} = 1951 cm^{-1}), and mass spectra. The structures and their systematic names are listed in the Supporting Information section. Dimerization of the ketene, and subsequent decarboxylation of the resulting *beta*-lactone in the presence of triethylamine to provide the allene, was described in detail for *tert*-butylcyanoketene.[25] In the present case, the proposed *beta*-lactone intermediate (**14**, Scheme 3) can be formed as a mixture of up to 8 possible diastereomers (three stereogenic carbon centers and two alkene geometries), but otherwise the transformations are analogous. Triethylamine was proposed[25] to promote the decarboxylation by nucleophilic addition to the lactone carbonyl carbon, followed by C-C cleavage and then elimination of $O(C{=}O)NEt_3$.

Crystals of the racemic major allene isomer of **15**, mp 226.0–226.7 °C, formed from hexane – ethyl acetate solution during the chromatography of the allene fraction derived from reaction of **7**. X-ray crystallographic analysis indicated this to be the diasteriomer shown in Scheme 3, derived from combination of **7** (with configuration at C-3 = *S*) and its enantiomer (C-3 = *R*).

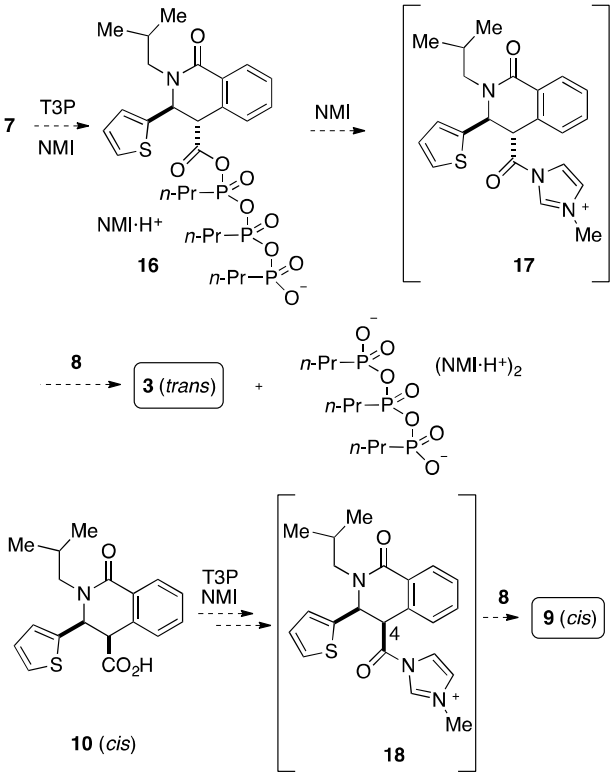
Scheme 3. Ketene and Derived Products Following T3P Activation



The amidation results with NMI as the base can be understood in light of the well-appreciated properties of NMI as an acyl transfer catalyst (Scheme 4).[26] The mixed anhydride intermediate **16** can be intercepted by NMI to give an activated acyl species **17**, and reaction of **17** with aniline **8** ought to be fast, leading efficiently to product **3**. The results with pyridine, which can also act as an acyl transfer promoter,[27] show it to be almost as effective (Table 1, entry 8). An even more powerful acyl transfer promoting combination, DMAP and triethylamine, nevertheless led to inferior stereochemical results (Table 1, entry 5), possibly as the result of the greater basicity. Starting from the *cis* acid **10**, an analogous set of steps leads to the activated *cis* acyl species **18**, and displacement provides the *cis* amide **9**. Because an appreciable amount of *trans* amide **3** forms from the *cis* acid **10** (Table 2, entry 3), some NMI-promoted *cis* to *trans* epimerization at C-4 must occur along the way. Three possibilities were considered: (A) the starting *cis* acid **10** itself might epimerize when exposed to NMI under these conditions – the NMI-promoted synthesis

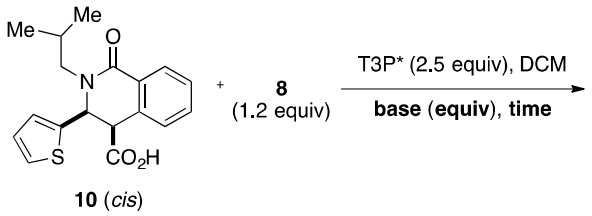
of the *trans* acid **7** features just such a process over 24 h; (B) epimerization of the product *cis* amide **9** to *trans* amide **3** might also be possible over the time frame of the amidation; and (C) the *cis* to *trans* epimerization of an intermediate might occur.

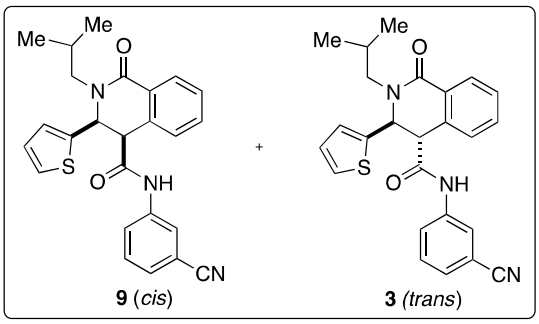
Scheme 4. Proposed Mechanism for T3P Amidation With NMI



Control experiments with *cis* acid **10** and 4 equiv of base (NMI, DABCO, and Et_3N, respectively) alone in CD_2Cl_2 solution established, according to H-1 NMR analysis, than no isomerization to *trans* acid **7** occurred over 60 min at room temperature, ruling out possibility A, above. To check whether post-amidation isomerization of *cis* amide **9** accounts for the significant proportion of (*trans*) **3** in the NMI promoted amidation of (*cis*) **10**, and whether formation of some of the *trans* product **3** seen in *cis*-selective Et_3N amidations is the result of product isomerization, an *in situ* H-1 NMR study was carried out on the triethylamine and NMI promoted T3P amidations in CD_2Cl_2 solution, starting with the *cis* acid **10** (Table 3). Three reactions were examined that used 2, 4, and 14 equiv of triethylamine, respectively, as the base, and a fourth reaction that used 2 equiv of NMI. These were monitored at 23 °C over 18 h of reaction time. The formation of *cis* and *trans* products, **9** and **3** respectively, was apparent from the diagnostic H-3 and H-4 signals in the spectrum of the crude reaction mixture: doublets (J = 5.7 Hz) in the case of **9**, and broad singlets (J < 1 Hz) for **3**.

Table 3. T3P Amidations – Stereochemistry of Triethylamine Mediation





Entry	Base	Equiv	Time	**9** : **3**[a]
1	Et_3N	2	3 min	3.3
2	Et_3N	2	36 min	2.9
3	Et_3N	2	18 h	3.5
4	Et_3N	4	9 min	7.0
5	Et_3N	4	39 min	6.5
6	Et_3N	4	18 h	8.0
7	Et_3N	14	11 min	8.5
8	Et_3N	14	36 min	8.8
9	Et_3N	14	18 h	8.0
10	NMI	2	9 min	1.6
11	NMI	2	38 min	1.6
12	NMI	2	18 h	1.5

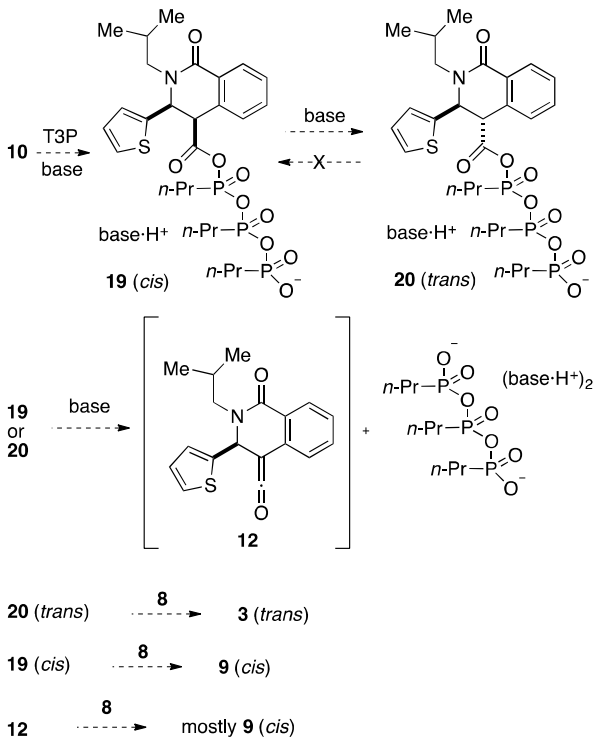
[a] *Cis*/*trans* product ratio as determined by *in situ* H-1 NMR analysis on CD_2Cl_2 solutions

Three qualitative features of the triethylamine data (entries 1–9) are apparent: (1) different amounts of triethylamine result in different *cis*/*trans* product ratios (more base gives more *cis*) although the less stable *cis* is favored in each case, (2) the *cis*/*trans* product ratios observed *in situ* are higher than the ratios

of isolated products from reactions run under the same conditions starting from the *trans* acid **7**, and (3) the *cis*/*trans* product ratios remain about the same over the course of the reaction. The last observation rules out *in situ* isomerization of the *cis* amide **9** by the action of triethylamine (possibility B, above). Likewise, the NMI mediated amidation shows no indication of product isomerization over 18 h (entries 10–12). Additionally, the NMR analysis indicates that both sets of amidation reactions are essentially complete within 10 min. Aqueous quench and extractive workup does not change the *cis*/*trans* ratios significantly.

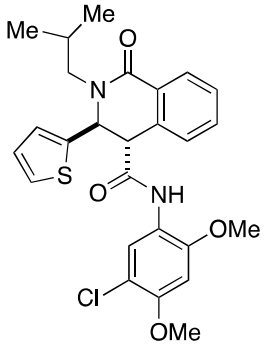
Ketene formation may not account entirely for the high proportions of *cis* product **9** in the triethylamine reactions of *cis* acid **10**, since the *cis*/*trans* ratios can exceed 5.6:1 (the result with DABCO, Table 2, entry 1). Scheme 5 outlines various T3P mediated processes that can lead to product in the presence of base. The portion of *cis* amide product **9** that does not arise from ketene **12** is formed by direct displacement of tris(phosphonate) dianion from **17** by aniline **8**. For the reaction of *cis* **10** in the presence of 2 equiv of triethylamine (Table 3, entries 1–3), somewhat more *trans* product is formed than would be expected from the ketene intermediate. This observation can be accounted for by proposing the isomerization of the phosphonate carboxylate mixed anhydride intermediate **17** to **18** (possibility C, above) which can only occur in the direction shown (*cis* to *trans*). A similar process was postulated to account for the racemization of amino acid derived amides reported by the Pfizer group.[20] Direct displacement of tris(phosphonate) dianion from **18** by aniline **8**, as seen earlier from the reaction of *trans* acid **7** (Scheme 2), could then provide a portion of *trans* amide **3**. Amounts of triethylamine greater than 2 equiv would logically lead to more ketene **12**, the formation of which can take place from either **17** or **18**. The *cis* to *trans* isomerization of a (presumably short-lived) *N*-acylammonium salt analogous to **18** (Scheme 3) could also conceivably contribute to the formation of *trans* amide product, although elimination and displacement would seem to be more likely fates because of the excellent leaving group.

Scheme 5. Proposed Mechanism for T3P Amidation of the *Cis* Acid 10

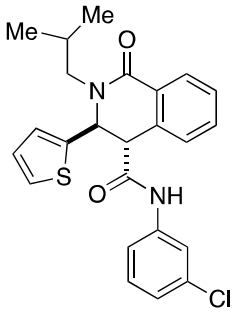


Because we required a wider series of tetrahydroquinolonic carboxanilides for our medicinal chemistry studies,[7] we applied the T3P/NMI conditions to the condensation of several additional anilines with carboxylic acids **7**, **6**, and **4**.[28] The resulting amides are displayed in Chart 1 along with isolated yields. The pyrazol-4-yl substrate **6** performed poorly, giving **2** in only 11% yield. As before (Scheme 1), interference by the pyrazole heteroatoms is implicated. For two examples, **24** and **1**, the reactions were successful when run in pure ethyl acetate as solvent. In the latter case, **4** was used as the starting acid, and 1 equiv of pyridine sufficed as the base.

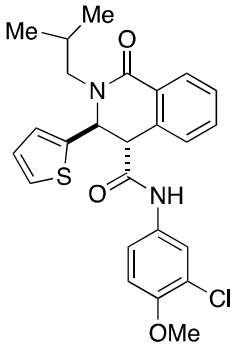
Chart 1. T3P Amidation Scope with Various Anilines



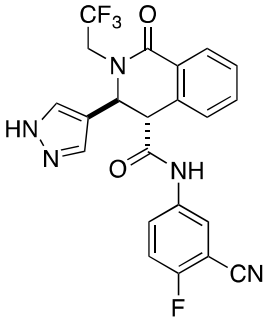
21 (91%)



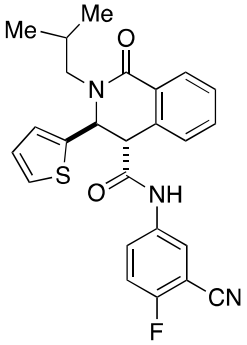
22 (88%)



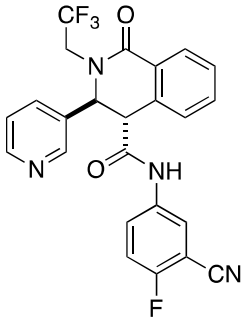
23 (73%)



2 (11%)



24 (85%)
solvent = ethyl acetate



1 (92%)
base = pyridine (1 equiv)
solvent = ethyl acetate

Conclusion

Efficient and potentially scalable amidation reactions of 1,2,3,4-tetrahydroisoquinol-2-onic 4-carboxylic acids **4**, **6**, **7**, and **10** with various anilines are achieved by using T3P as the coupling reagent. The conversions proceed by way of mixed anhydride intermediates, for example, **19** (*cis*) and **20** (*trans*), which can themselves follow displacement, epimerization/displacement, or elimination/addition pathways

to carboxamide product. From the *trans* acid, the latter (ketene) pathway gives mostly the *cis* amide, whereas displacement with NMI or pyridine acting as a presumed acyl transfer agent affords good isolated yields of the *trans* amide.

Experimental Section

(3*S,4*S**)-*N*-(3-Cyano-4-fluorophenyl)-1-oxo-3-(pyridin-3-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (1).[7] (A) With $POCl_3$.** A solution of carboxylic acid[9] **4** (10 g, 28.6 mmol) and 5-amino-2-fluorobenzonitrile (**5**, 5.82 g, 42.8 mmol, 1.5 equiv) in 400 mL of acetonitrile was treated with phosphorus(V) oxychloride ($POCl_3$, 2.95 mL, 31.4 mmol, 1.1 equiv), and the solution was heated at 85 °C for 15 h. The reaction mixture was cooled, concentrated to about 150 mL, and then treated with aq sodium dihydrogen phosphate (66 g in 500 mL of water). The suspension was stirred overnight and then filtered. The resulting solid was air dried to afford the carboxamide **1** as a beige colored solid (12.9 g, 96%), mp 210–212 °C: ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.11 (dd, 1 H, J = 7.6 and 1.4 Hz), 7.98 (dd, 1 H, J = 5.6 and 2.7 Hz), 7.86 (ddd, 1 H, J = 9.2, 4.7, and 2.7 Hz), 7.58 (td, 1 H, J = 7.6 and 1.2 Hz), 7.52 (td, 1 H, J = 7.6 and 1.2 Hz), 7.37 br s, 1 H), 7.37 (t, 1 H, J = 9.2 Hz), 7.33 (d, 1 H, J = 8.2), 7.26 (br s, 1 H), 5.41 (d, 1 H, J = 1.8 Hz), 4.74 (dq, 1 H, J = 15.2 and 9.2 Hz), 4.21 (d, 1 H, J = 2.0 Hz), 3.80 (dq, 1 H, J = 15.2 and 9.2 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ 169.4, 165.3, 159.5 (d, J = 253 Hz), 135.7 (d, J = 3 Hz), 134.6, 133.1, 129.3, 128.8, 128.6, 128.0, 127.1 (d, 2 C's, J = 8 Hz), 124.9 (q, J = 278 Hz), 124.3 (2 C's), 119.5, 116.8, 116.7 (d, J = 21 Hz), 113.3, 100.9 (d, J = 16 Hz), 56.9, 52.5, 46.2 (q, J = 34 Hz); HR–ESI–MS $[M+H]^+$ calcd for $C_{22}H_{16}F_4N_5O_2$, 458.1240; found, 458.1241.

(B) With T3P and pyridine. A solution of acid **4** (122 mg, 0.348 mmol, 1 equiv), 3-amino-2-fluorobenzonitrile (**5**, 57 mg, 0.418 mmol, 1.2 equiv), and pyridine (0.028 mL, 0.348 mmol, 1 equiv) in ethyl acetate (12 mL) was stirred at 0 °C. *n*-Propanephosphonic acid anhydride (T_3P, 50% solution in ethyl acetate, 554 mg, 0.871 mmol, 2.5 equiv) was added by drops. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was concentrated under reduced pressure, diluted with water, and the product was extracted with dichloromethane (2 X 10 mL). The organic solution was dried over anhydrous sodium sulfate and concentrated. Chromatography on silica by using 10%–50% ethyl acetate in hexane as the eluant afforded 150 mg (92%) of **1**.

(3*S,4*S**)-*N*-(3-Cyanophenyl)-2-isobutyl-1-oxo-3-(pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (2).[7] (A) With $POCl_3$.** A solution of carboxylic acid[9] **6** (448 mg, 1.32 mmol), aniline **5** (269 mg, 1.98 mmol, 1.5 equiv), and phosphoryl chloride (0.136 mL, 1.45 mmol, 1.1 equiv) in 20 mL of acetonitrile was heated at reflux for 3 h. The reaction mixture was quenched by pouring into ice water, and then extracted with ethyl acetate. The organic solution was washed with aqueous sodium

carbonate, dried, and then concentrated. The crude product was purified by chromatography on silica by using 20–100% ethyl acetate / hexane mixtures as the eluant to afford 420 mg (70%) of carboxanilide **2** as an off-white solid, mp 197–199 °C: ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.11 (dd, 1 H, *J* = 7.6 and 1.4 Hz), 7.98 (dd, 1 H, *J* = 5.6 and 2.7 Hz), 7.86 (ddd, 1 H, *J* = 9.2, 4.7, and 2.7 Hz), 7.58 (td, 1 H, *J* = 7.6 and 1.2 Hz), 7.52 (td, 1 H, *J* = 7.6 and 1.2 Hz), 7.37 br s, 1 H), 7.37 (t, 1 H, *J* = 9.2 Hz), 7.33 (d, 1 H, *J* = 8.2 Hz), 7.26 (br s, 1 H), 5.41 (d, 1 H, *J* = 1.8 Hz), 4.74 (dq, 1 H, *J* = 15.2 and 9.2 Hz), 4.21 (d, 1 H, *J* = 2.0 Hz), 3.80 (dq, 1 H, *J* = 15.2 and 9.2 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ 169.4, 165.3, 159.5 (d, *J* = 253 Hz), 135.7 (d, *J* = 3 Hz), 134.6, 133.1, 129.3, 128.8, 128.6, 128.0, 127.1 (d, 2 C's, *J* = 8 Hz), 124.9 (q, *J* = 278 Hz), 124.3 (2 C's), 119.5, 116.8, 116.7 (d, *J* = 21 Hz), 113.3, 100.9 (d, *J* = 16 Hz), 56.9, 52.5, 46.2 (q, *J* = 34 Hz); HR–ESI–MS $[M+H]^+$ calcd for $C_{22}H_{16}F_4N_5O_2$, 458.1240; found, 458.1241.

(B) With T3P and NMI. The amide was also prepared from **6** (100 mg, 0.295 mmol) by following the procedure for **3**, below, providing **2** (15 mg, 11%) as an off-white solid, mp 197–199 °C.

(3*S,4*S**)-*N*-(3-Cyanophenyl)-2-isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (3).**[7] A solution of 1-methyl-1H-imidazole (NMI, 0.21 mL, 0.608 mmol, 2 equiv), carboxylic acid[9] **7** (100 mg, 0.304 mmol, 1 equiv) and 3-aminobenzonitrile (**8**, 43 mg, 0.364 mmol, 1.2 equiv) in dichloromethane (5 mL) was stirred at 0 °C. *n*-Propanephosphonic acid anhydride (T_3P, 50% solution in ethyl acetate, 483 mg, 0.76 mmol, 2.5 equiv) was added, and the reaction mixture was allowed to warm to room temperature and to stir for 16 h. The reaction mixture was diluted with dichloromethane and the organic solution was washed successively with saturated aqueous sodium bicarbonate, water and brine, and then dried over anhydrous sodium sulfate. Concentration followed by chromatography on silica with 10%–50% ethyl acetate in hexane as the eluant afforded 119 mg (91%) of the carboxamide **3**, R_f = 0.40 (2:1 hexane / ethyl acetate). A sample crystallized from ethyl acetate had mp 239.9–240.0 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1 H), 8.03 (s, 1 H), 7.94 (d, 1 H, *J* = 7.4 Hz), 7.81 (d, 1 H, *J* = 6.9 Hz), 7.56 (t, 2 H, *J* = 7.2 Hz), 7.42 – 7.51 (m, 2 H), 7.34 (d, 1 H, *J* = 7.2 Hz), 7.30 (d, 1 H, *J* = 5.0 Hz), 7.01 (d, 1 H, *J* = 3 Hz), 6.90 (t, 1 H, *J* = 4.1 Hz), 5.47 (s, 1 H), 4.33 (s, 1 H), 3.78 (dd, 1 H, *J* = 13.2 and 8.8 Hz), 2.63 (dd, 1 H, *J* = 13.4 and 5.8 Hz), 1.84 – 1.90 (m, 1 H), 0.79 (q, 6 H, *J* = 6.1 Hz), 0.80 (d, 3 H, *J* = 6.8 Hz), 0.77 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 162.9, 143.6, 139.7, 133.8, 132.0, 130.4, 130.1, 128.8, 128.1, 127.3, 127.2, 126.5, 126.3, 125.6, 123.9, 122.0, 118.6, 111.6, 58.5, 52.5, 51.7, 27.2, 20.15, 20.13; HR–ESI–MS $[M+H]^+$ calcd for $C_{25}H_{24}N_3O_2S$, 430.1589; found, 430.1591.

(3*S,4*R**)-*N*-(3-Cyanophenyl)-2-isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (9).**[7] **(A) From (*cis*) 10 with triethylamine as the base.** A solution of *cis* carboxylic acid **10** (318 mg, 0.965 mmol), aniline **8** (228 mg, 1.931 mmol, 2.0 equiv), and

triethylamine (0.538 mL, 3.86 mmol, 4 equiv) in 16 mL of dichloromethane was stirred at 0 °C. Propane-1-phosphonic acid anhydride (T_3P, 50% solution in ethyl acetate, 1.533 mg, 2.413 mmol, 2.5 equiv) was added by drops. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h. Concentration and chromatography on silica by using 20–100% ethyl acetate / hexane mixtures as the eluant afforded 42 mg (10%) of *trans* amide **3** and 274 mg (69%) of *cis* amide **9** as a white solid, mp 229–230 °C, R_f = 0.35 (2:1 hexane / ethyl acetate): ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.01 (d, 1 H, J = 7.5 Hz), 7.97 (s, 1 H), 7.75 (d, 1 H, J = 8 Hz), 7.57 (t, 1 H, J = 7.5 Hz), 7.42 – 7.52 (m, 3 H), 7.40 (d, 1 H, J = 7.5 Hz), 7.20 (d, 1 H, J = 5.5 Hz), 6.85 – 6.90 (m, 1 H), 6.80 – 6.85 (m, 1 H), 5.39 (d, 1 H, J = 6.0 Hz), 4.79 (d, 1 H, J = 6.0 Hz), 3.85 (dd, 1 H, J = 8.5 and 14 Hz), 2.76 (dd, 1 H, J = 8.0 and 14 Hz), 2.10 – 2.22 (m, 1 H), 0.90 – 1.00 (m, 6 H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 168.0, 164.7, 139.5, 139.3, 134.1, 132.5, 130.0, 129.0, 128.13, 128.10, 127.92, 127.90, 127.6, 126.1, 125.8, 124.4, 123.1, 118.2, 112.7, 59.3, 52.9, 50.8, 27.3, 19.5, 19.4; HR–ESI–MS $[M+H]^+$ calcd for $C_{25}H_{24}N_3O_2S$, 430.1589; found, 430.1589.

(B) From (*cis*) 10 with DABCO as the base. A solution of *cis* carboxylic acid **10** (100 mg, 0.304 mmol, 1 equiv), aniline **8** (43 mg, 0.364 mmol, 1.2 equiv), and DABCO (136 mg, 1.214 mmol, 4 equiv) in dichloromethane (10 mL) was stirred at 0 °C. Propane-1-phosphonic acid anhydride (50% solution in ethyl acetate, 483 mg, 0.759 mmol, 2.5 equiv) was added by drops. The reaction mixture was then warmed to room temperature and stirred for 16 h. Workup as for **9** above afforded a crude product mixture, and chromatography on silica by using 20–100% ethyl acetate / hexane mixtures as the eluant afforded in order of elution 16 mg (12%) of the *trans* amide **3** and 85 mg (65%) of the *cis* amide **9**.

(C) From (*cis*) 10 with NMI as the base. C*is* acid **10** was combined with aniline **8** according to the same reagent amounts and procedure as described above in (B) except that 1-methyl-1H-imidazole (0.048 mL, 0.607 mmol, 2 equiv) was used as the base. Workup and chromatography as before gave 64 mg (49%) of the *trans* amide **3** and 58 mg (44%) of the *cis* amide **9**.

(D) From (*trans*) 7 with DABCO as the base. The amidation of *trans* acid **7** with DABCO as the base according to the same reagent amounts and procedure as described above in (B) afforded 16 mg (12%) of the *trans* amide **3** and 87 mg (67%) of the *cis* amide **9**.

(3*S,4*R**)-2-Isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (10).**[7] A stirred solution of (*Z*)-*N*-isobutyl-1-(thiophen-2-yl)methanimine (1.0 g, 5.18 mmol, 1 equiv) in 15 mL of dichloromethane was cooled to –30 °C (external temperature, dry ice / acetone bath), and then treated with homophthalic anhydride (0.84 g, 5.18 mmol, 1 equiv) in one portion. The reaction mixture was stirred at –30 °C for 2.5 h, then was allowed to warm to room temperature and to stir for an additional 16 h. Filtration gave the *cis* carboxylic acid, **10**, as a white solid (0.98 g, 57% yield), mp 199.1–200.6 °C: ^{1}H NMR (300 MHz, MeOH-d_4) δ 8.07 (d, J = 7.8 Hz, 1 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.58 (t, J = 7.5 Hz, 1 H),

7.48 (td, *J* = 7.6 and 0.9 Hz, 1 H), 7.17 (d, *J* = 5.1 Hz, 1 H), 6.92 (d, *J* = 3.3 Hz, 1 H), 6.84 (td, *J* = 5.1 and 0.9 Hz, 1 H), 5.42 (d, *J* = 5.4 Hz, 1 H), 4.77 (d, *J* = 5.4 Hz, 1 H), 3.88 (dd, *J* = 13.0 and 7.8 Hz, 1 H), 2.76 (dd, *J* = 13.0 and 7.8 Hz, 1 H), 2.08 – 2.22 (m, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.5, 163.2, 140.3, 134.1, 132.3, 129.6, 128.5, 128.4, 127.9 (2 C's), 126.7, 126.3, 58.4, 53.0, 48.3, 27.4, 20.6, 20.5; HPLC: 97.8% purity; HR–ESI–MS $[M+H]^+$ calcd for $C_{18}H_{20}NO_3S$, 330.1164; found, 330.1166.

Monitoring Amidations by H-1 NMR Spectroscopy (Table 3). A solution of the *cis* acid **10** (approximately 5 mg, 1 equiv), 3-aminobenzonitrile (1.2 equiv), and base (triethylamine or NMI, 2–14 equiv) in 0.5 mL of dichloromethane-d_2 in an NMR tube was treated with T3P (50% solution in ethyl acetate, 2.5 equiv). An H-1 NMR spectrum was taken right away, and the reaction was monitored periodically by NMR analysis over 18 h of reaction time. The respective diagnostic doublets for H-3 and H-4 of amide products **9** and **3** were apparent at 4.3–5.5 ppm; integration of these signals gave the product ratios.

Allenes 15. (A) From *cis* Acid 10. A solution of *cis* carboxylic acid **10** (106 mg, 0.322 mmol) and triethylamine (179 μL, 1.29 mmol, 4 equiv) in dichloromethane (5 mL) was stirred at 0 °C. A 50% solution of T3P in ethyl acetate (447 μL, 0.76 mmol, 2.5 equiv) was added by drops, and the resulting solution was stirred at 0 °C for 10 min, and then was allowed to warm to room temperature and stir for 16 h. The reaction mixture was concentrated, and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was concentrated to a residue and chromatographed on silica gel with 4:1 hexane / ethyl acetate as the eluant to afford the mixture of allenes **15** as a white powder, 56 mg (60%), R_f = 0.31 (4:1 hexane / ethyl acetate). ^{1}H NMR analysis indicates that **15** comprises a 26:5:4 mixture of three diastereomers (H-3 signals at 5.62, 5.65, and 5.59 ppm respectively). Structures and systematic names of the three allene diasteriomers are given in Supporting Information. Symmetry considerations dictate that the two minor isomers should have structurally equivalent tetrahydroisoquinoline halves, whereas in the major isomer (see below) the halves are non-equivalent. The latter distinction is apparent in the C-13 NMR spectrum. For example, four C=O resonances are observed – the two most prominent (163.05 and 162.9 ppm) belong to the major isomer, and the two less prominent (163.3 and 163.14 ppm) belong to the two minor isomers. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.20 – 8.27 (m, 1H), 7.16 – 7.46 (m, 4 H), 6.76 – 7.10 (m, 2 H), 5.65, 5.62, and 5.59 (three br s, respective ratio 5:26:4 by integration), 4.09 – 4.35 (m, 1.3 H), 2.62 – 2.73 (1 H), 2.05 – 2.24 (1.1 H), 1.04, 1.00, 0.92, 0.90 (four d of major isomer, *J* = 6.7 Hz), 1.09, 1.056, 1.04, 1.005 (four d of two minor isomers, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.8, 200.0, 163.3, 163.14, 163.05, 162.9, 144.4, 144.1, 143.8, 143.8, 132.6, 132.4, 130.3, 130.1, 129.13, 129.09, 128.95, 128.91, 128.7, 127.9, 127.1, 126.9, 126.8, 126.5, 126.1, 125.38, 125.35, 125.27, 125.0, 108.3, 107.6, 107.5, 107.4, 77.2, 60.6, 59.8, 59.3, 58.6, 54.0, 53.6, 53.5, 53.2, 27.6, 27.4, 27.23, 27.22, 20.6, 20.3, 20.23, 20.16,

20.13, 19.9; IR (KBr pellet) 1951 cm^{-1}; HR–ESI–MS $[M+H]^+$ calcd for $C_{35}H_{35}N_2O_2S_2^+$, 579.2140; found, 579.2126.

(B) From *trans* Acid 7. By the same procedure as in (A), above, 103 mg of **7** was treated with triethylamine and T3P. Chromatography of the crude product as above gave an allene fraction; a second chromatography with 5:1 hexane / ethyl acetate as the eluant afforded the same mixture of allenes **15** (when combined, 25.7 mg, 28%, 26:5:4 ratio by NMR analysis). From one of the fraction solutions, colorless crystals formed, ~ 3 mg, mp 226.0–226.7 °C, that proved to be suitable for X-ray crystallographic analysis (see Scheme 3 and Supporting Information). H-1 NMR analysis confirmed that this isomer corresponds to the major allene isomer in (A). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 – 8.28 (m, 1 H), 8.22 (ddd, 1 H, *J* = 0.5, 1.5, and 7.8 Hz), 7.42 – 7.45 (m, 2 H), 7.40 (dt, 1 H, *J* = 1.5 and 7.5 Hz), 7.29 (dt, 1 H, *J* = 1.5 and 7.5 Hz), 7.23 – 7.25 (m, 1 H), 7.22 (dd, 1 H, *J* = 1.3 and 4.5 Hz), 7.19 (dd, 1 H, *J* = 1.5 and 4.8 Hz), 6.96 (ddd, 1 H, *J* = 0.5, 1.3, and 7.5 Hz), 6.87 – 6.90 (m, 4 H), 5.62 (br s, 2 H), 4.23 (dd, 1 H, *J* = 7.5 and 12.5 Hz), 4.16 (dd, 1 H, *J* = 7.5 and 12.5 Hz), 2.65 (dd, 2 H, *J* = 7.5 and 12.7 Hz), 2.05 – 2.20 (m, 2 H), 1.04, 1.00, 0.92, 0.90 (four d, 12 H, *J* = 6.7 Hz).

(3*S,4*S**)-*N*-(5-Chloro-2,4-dimethoxyphenyl)-2-isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (21).** This amide was prepared from **7** (50 mg, 0.152 mmol) by following the procedure for **3**, above, providing **21** (69 mg, 91%) as a foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.40 (m, 2 H), 7.6 – 7.7 (m, 2 H), 7.38 – 7.43 (m, 1 H), 7.31 (dd, 1 H, *J* = 6.6 and 1.8 Hz), 7.09 (dd, 1 H, *J* = 4.8 and 1.2 Hz), 6.83 – 6.86 (m, 2 H), 6.35 (s, 1 H), 5.76 (s, 1 H), 4.04 (s, 1 H), 4.01 (dd, 1 H, *J* = 13.6 and 10 Hz), 3.83 (s, 3 H), 3.57 (s, 3 H), 2.71 (dd, 1 H, *J* = 13.6, 8.4 Hz), 2.01 – 2.14 (m, 1 H), 0.91 (d, 3 H, *J* = 6.8 Hz), 0.76 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ 168.9, 164.5, 153.0, 150.1, 143.8, 134.4, 133.4, 130.5, 130.0, 129.5, 128.7, 127.1, 126.8, 125.9, 122.7, 120.9, 112.9, 97.9, 59.5, 56.6, 56.6, 56.5, 53.5, 53.4, 27.9, 20.3, 20.3, 20.2; HR–ESI–MS $[M+Na]^+$ calcd for $C_{26}H_{27}ClN_2NaO_4S$, 521.1278; found, 521.1277.

(3*S,4*S**)-*N*-(3-Chlorophenyl)-2-isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (22).**[7] This amide was prepared from **7** (50 mg, 0.152 mmol) by following the procedure for **3**, above, providing **22** (59 mg, 88%) as a foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (br s, 1 H), 7.94 (dd, 1 H, *J* = 7.6 and 1.2 Hz), 7.76 (t, 1 h, *J* = 2.0 Hz), 7.45 – 7.51 (m, 3 H), 7.29 – 7.36 (m, 3 H), 7.10 (d, 1 H, *J* = 7.6 Hz), 7.02 (d, 1 H, *J* = 3.2 Hz), 6.90 (dd, 1 H, *J* = 5.2 and 3.6 Hz), 5.49 (s, 1 H), 4.30 (s, 1 H), 3.79 (dd, 1 H, *J* = 13.2 and 8.8 Hz), 2.63 (dd, 1 H, *J* = 13.2 and 6.0 Hz), 1.85 – 1.93 (m, 1 H), 0.82 (d, 3 H, *J* = 6.8 Hz), 0.78 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 163.0, 142.5, 137.8, 134.6, 133.1, 132.0, 130.0, 129.9, 129.8, 129.5, 129.3, 126.6, 125.9, 125.2 (2 C), 120.2, 118.1, 58.4, 54.3, 52.9, 27.3, 20.2, 20.0; HR–ESI–MS $[M+H]^+$ calcd for $C_{24}H_{24}ClN_2O_2S$, 439.1247;

found, 439.1241.

(3*S,4*S**)-*N*-(3-Chloro-4-methoxyphenyl)-2-isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (23).**[7] This amide was prepared from **7** (150 mg, 0.455 mmol) by following the procedure for **3**, above, providing **23** (153 mg, 73%) as a foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.31 (m, 1 H), 7.59 – 7.62 (m, 2 H), 7.29 – 7.33 (m, 2 H), 7.17 (d, 1 H, *J* = 2.8 Hz), 7.08 – 7.15 (m, 1 H), 6.80 – 6.84 (m, 3 H), 6.72 (s, 1 H), 5.76 (s, 1 H), 3.99 – 4.05 (m, 2 H), 3.85 (s, 3 H), 2.66 – 2.79 (m, 1 H), 2.01 – 2.18 (m, 1 H), 0.93 (d, 3 H, *J* = 6.8 Hz), 0.82 (d, 3 H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.6, 163.3, 151.1, 144.1, 134.5, 132.9, 132.3, 130.5, 129.2, 128.8, 128.4, 127.6, 126.9, 126.6, 126.0, 121.5, 121.0, 119.7, 113.4, 59.0, 56.6, 52.9, 52.1, 27.6, 20.61, 20.59; HR–ESI–MS $[M+Na]^+$ calcd for $C_{25}H_{25}ClN_2NaO_3S$, 491.1172; found, 491.1168.

(3*S,4*S**)-*N*-(3-Cyano-4-fluorophenyl)-2-isobutyl-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (24).**[7] This amide was prepared from **7** (50 mg, 0.152 mmol) by following the procedure for **3**, above, providing **24** (58 mg, 85%) as a foam: ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.06 (d, 1 H, *J* = 7.2 Hz), 7.95 – 8.00 (m, 1 H), 7.79 - 7.85 (m, 1 H), 7.43 – 7.56 (m, 2 H), 7.25 – 7.33 (m, 2 H), 7.18 (d, 1 H, *J* = 5.2 Hz), 6.95 (d, 1 H, *J* = 2.8 Hz), 6.86 (t, 1 H, *J* = 4.2 Hz), 5.52 (s, 1 H), 4.25 (s, 1 H), 3.88 (dd, 1 H, *J* = 13.2 and 8.8 Hz), 2.77 (dd, 1 H, *J* = 13.6 and 6.0 Hz), 1.90 – 2.10 (m, 1 H), 0.89 (d, 6H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, MeOH-d_4) δ 169.5, 164.9, 160.8, 158.2, 142.9, 135.7, 133.5, 132.6, 130.0, 128.9, 128.6, 127.8, 127.1, 126.2, 125.3, 124.3, 116.8 (br), 113.3, 100.9, 59.4, 53.4, 52.8, 27.7, 19.63, 19.58; HR–ESI–MS $[M+H]^+$ calcd for $C_{25}H_{23}FN_3O_2S$, 448.1495; found, 448.1494.

Acknowledgment. We are grateful to NIH (AI090662) and Medicines for Malaria Venture for financial support, and to Jaeki Min, Lei Yang, and Haiyan Zheng for analytical assistance.

Supporting Information: Scanned ^{1}H and ^{13}C NMR spectra of new compounds, including stereochemistry and systematic names for isomers of **15**, and CIF for **15**. This material is available free of charge via the Internet at http://pubs.acs.org/.

References and Notes

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