VIP Amine Synthesis

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Tantalum–Amidate Complexes for the Hydroaminoalkylation of Secondary Amines: Enhanced Substrate Scope and Enantioselective Chiral Amine Synthesis**

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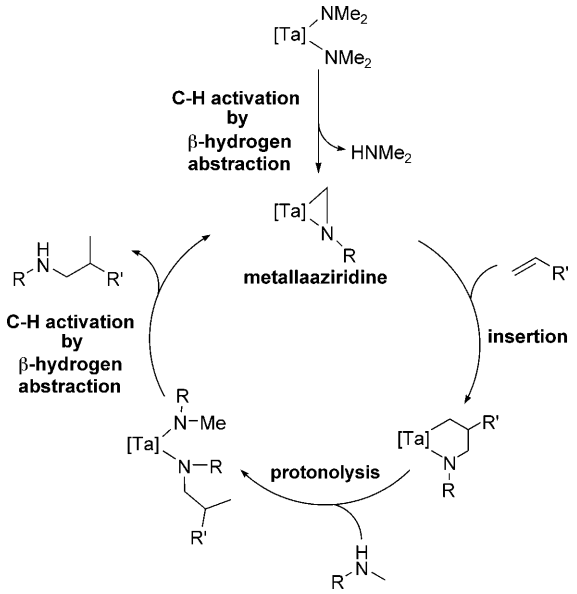
The catalytic synthesis of chiral amines is important in the rapid and selective assembly of useful building blocks for the pharmaceutical, agrochemical, and fine chemical industries. Recent research efforts have focused on the addition of N–H bonds across C–C multiple bonds, the hydroamination reaction.[1] An emerging alternative approach is the α-alkylation of amines, the hydroaminoalkylation reaction, which is a catalytic C–C bond-forming reaction α to a nitrogen atom.[2–6] The α-alkylation of amines is a complementary catalytic strategy for the synthesis of amines that is 100% atom economic. Herein we disclose the first examples of auxiliary ligand supported tantalum complexes for regioselective and diastereoselective hydroaminoalkylation. We show that tunable and modular amidate tantalum complexes promote the facile formation of tantallaaziridines, a previously unobserved catalytically active intermediate.[3,4] This class of complexes shows expanded substrate scope over all previously reported systems[4,5] and most importantly, it is the first example of a chiral tantalum–amidate precatalyst for enantioselective amine synthesis by hydroaminoalkylation.

Pioneering work from the early 1980s[2,3] inspired Herzon and Hartwig to carry out a detailed study of Ta^{V} amido derivatives as catalysts for the α-alkylation of alkylaryl[4a] and dialkyl[4b] amines with terminal and activated alkene substrates. In ligand screening investigations they showed that many typical early transition-metal ligand sets (e.g., Cp, alkoxide, chelating amide) dramatically reduce catalytic activity,[4] whereas electron-withdrawing chloride ligands promote the generation of electrophilic and catalytically active complexes.[4b] Our research group has previously applied easily varied amidates for the synthesis of electrophilic catalysts.[7] Recently, we showed that Group 4 amidate based systems can cyclize primary aminoalkenes to produce primary amine substituted carbocycles by an intramolecular hydroaminoalkylation reaction.[8] However, intermolecular variants of this reaction remain elusive with our Zr precatalyst. In contrast, Doye and co-workers demonstrated that inexpensive Ti^{IV} complexes are competent catalysts for the catalytic α-alkylation of both primary and secondary amines for intra- and intermolecular reactions using a select group of substrates.[5] Notably, in all these catalytic reactions, metallaaziridines have been proposed as the catalytically active species (e.g., Scheme 1).



Scheme 1. Proposed mechanism involving a tantallaaziridine intermediate.

Herein we disclose the preparation and characterization of the first mono- and bis(amidate)–tantalum complexes, and demonstrate their promise as flexible and tunable catalyst systems for the hydroaminoalkylation of secondary amines. These preliminary investigations show how the flexible amidate ligand framework can be used advantageously to achieve the selective synthesis of the branched product in a diastereo- and enantioselective fashion.

Initial efforts focused on the preparation of bis(amidate)–tantalum complexes, as we have observed bis(amidate) complexes of Group 3 and 4 metals to be outstanding catalysts for the hydroamination reaction.[7,9] In preparing the tantalum analogue, two equivalents of *N*-(2,6-dimethylphenyl)pivalamide were added to $[Ta(NMe_2)_5]$, and gratifyingly the tantallaaziridine complex **1** (Scheme 2) was formed spontaneously. Complex **1** was obtained as an analytically

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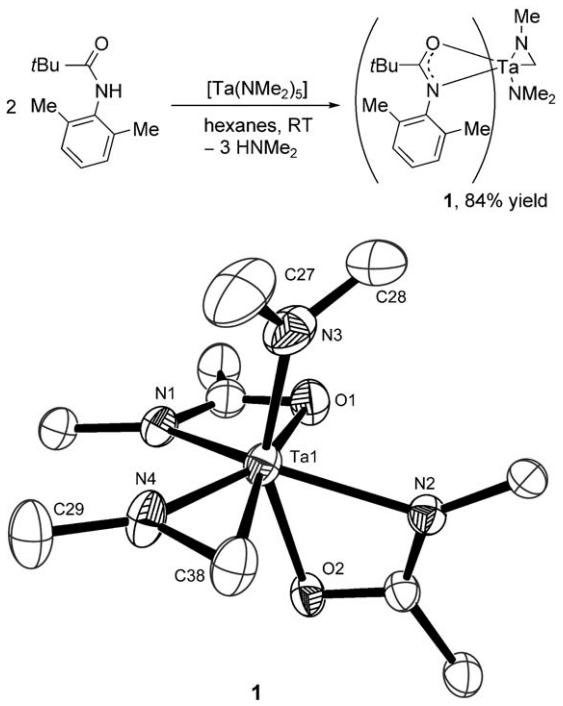


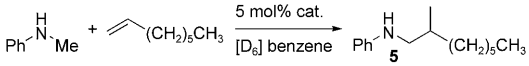
Scheme 2. Synthesis and ORTEP diagram of solid state molecular structure of **1**. Thermal ellipsoids depicted at 50% probability. All hydrogen atoms and most amidate ligand atoms omitted for clarity. Selected bond lengths [Å] and angles [°]: Ta1–N4 1.921(4), Ta1–N3 1.970(5), Ta1–C38 2.178(5), N4–C29 1.451(7), N4–C38 1.424(6), N3–C28 1.459(9), N3–C27 1.463(9), Ta1–N1 2.179(4), Ta1–N2 2.245(4), Ta1–O1 2.214(4), Ta1–O2 2.132(3); N4-Ta1-C38 40.04(17), Ta1-N4-C38 79.7(3), Ta1-N4-C29 155.8(4), Ta1-N3-C27 124.1(5), Ta1-N3-C28 123.0(4), N1-Ta1-O1 59.35(14), N2-Ta1-O2 59.34(12).

pure yellow crystalline solid in 84% yield, and diagnostic signals in the ^{1}H NMR spectrum for the diastereotopic metallaaziridine CH_2 protons are clearly observed as doublets at $\delta = 2.34$ and 2.49 ppm ($^2J_{H,H} = 3.5$ Hz), whereas the *N*-methyl of the metallaaziridine and the methyl signal of the dimethylamido ligand resonate at $\delta = 3.16$ and 3.07 ppm, respectively. The

X-ray crystallographic analysis of C_1 symmetric **1** reveals a cyclometalated *N*-methylenemethanamide fragment as depicted in Scheme 2 with a H_2C–N bond length within the range of lengths typical of C–N single bond. Most importantly, complex **1** has been found to be a competent precatalyst for the alkylation of *N*-methylaniline with 1-octene at 130 °C to give the known product **5** (Table 1, entry 1). Although spontaneous, stoichiometric tantallaaziridine formation has been previously disclosed,[10] such complexes have never been reported to be catalytically active. Previous to this work, in catalytically competent systems, such tantallaaziridine complexes had not been observed in either solution phase or solid state, although their formation has been proposed to be rate limiting in the catalytic cycle.[4a]

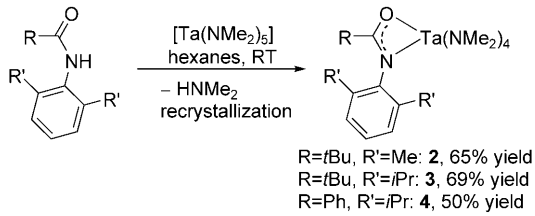
A variety of mono(amidate)–tantalum complexes can be easily prepared at ambient temperature in hexanes to give crystalline complexes **2**, **3**, and **4**, which have varying degrees of steric bulk (Scheme 3). Most importantly, a screen of complexes **1**–**4** as catalysts for the α-alkylation of *N*-methylaniline with 1-octene shows that mono(amidate)–tantalum complexes (Table 1, entries 2–5) allow reactions at a lower temperature (110 °C) compared to the parent bis(amidate) compound **1**. Whereas most mono(amidate)–tantalum complexes show reactivity at 110 °C, [Ta(NMe$_2$)$_5$] requires at least 130 °C to effect product formation (Table 1, entries 6 and 7).

Table 1: Catalyst screening of tantalum amido complexes.



Entry	Catalyst	Conditions	Conversion [%][a]
1	**1**[b]	130 °C, 1 week[c,d,e]	71
2	**2**	130 °C, 24 h[c,e,f]	84
3	**2**	110 °C, 68 h[c,f]	69
4	**3**	110 °C, 63 h[c,f]	96 (92)
5	**4**	110 °C, 77 h[c,f]	85
6	[Ta(NMe$_2$)$_5$]	110 °C[c,f]	n.r.
7	[Ta(NMe$_2$)$_5$]	130 °C, 67 h[c,f]	89 (80)

[a] Yield of isolated product given in brackets; conversion was estimated by ^{1}H NMR spectroscopy. [b] 10 mol%; [c] [*N*-methylaniline] = 1 M. [d] *N*-methylaniline/1-octene 1:1.05. [e] [D_8]toluene as solvent. [f] *N*-methylaniline/1-octene 1:1.5. n.r. = no reaction.

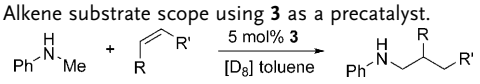


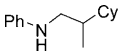
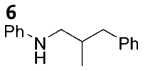
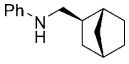
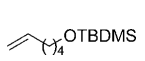
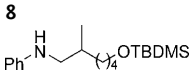
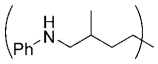
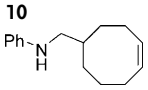
Scheme 3. Synthesis of mono(amidate)–tantalum tetrakis(dimethylamido) complexes with variable steric bulk.

The observed reactivity trends suggest that steric bulk is required to favor the β-hydrogen abstraction reaction, yet too much steric bulk appears to inhibit olefin insertion. This mechanistic interpretation would account for the ready formation of metallaaziridine **1**, as well as its overall reduced catalytic activity. Furthermore, this is consistent with the empirical observation that increased alkene loading (e.g., *N*-methylaniline/vinylcyclohexane (see below) 1:2.4 versus 1:1.2) results in improved relative rates of reaction in side-by-side NMR tube experiments. These early results show that sterically bulky mono(amidate)–tantalum complex **3** is the most efficient among the tested precatalysts and a more complete exploration of its substrate scope is presented herein (Table 2 and Table 3).

In alkene substrate scope investigations terminal alkenes having steric bulk, such as vinylcyclohexane, and easily isomerized allylbenzene form the corresponding α-alkylation products **6** and **7** in high product yields upon isolation. Norbornene, as an activated olefin, is efficiently converted into the corresponding product **8** with unprecedented diastereoselectivity (> 20:1) at 110 °C. Protected alcohols can be used to access silyl protected amino alcohol derivative **9**. Exposing 1,7-octadiene to the standard conditions while using 1.9 equivalents of *N*-methylaniline results in the synthesis of

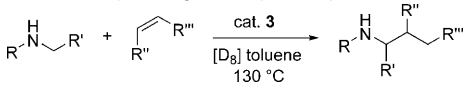
Table 2: Alkene substrate scope using **3** as a precatalyst.

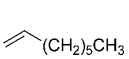
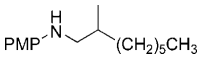
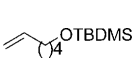
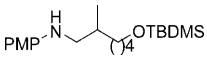
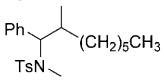
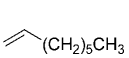
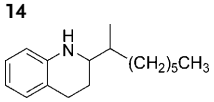
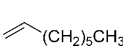
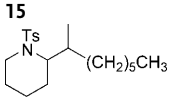


Entry	Alkene	Conditions	Product	Yield [%][a]
1		145 °C, 15 h[b,c]	 **6**	90
2		130 °C, 19 h[b,c]	 **7**	85
3		110 °C, 96 h[b,c]	 **8**	93[d]
4		130 °C, 11 h[b,c]	 **9**	85
5		130 °C, 19 h[e]	 **10**	75[f]
6		165 °C, 96 h[b,g]	 **11**	83

[a] Yield of isolated product. [b] [*N*-methylaniline] = 1 M; [c] *N*-methylaniline/1-octene 1:1.5. [d] A greater than 20:1 d.r. as estimated by NMR spectroscopy. [e] *N*-methylaniline/1,7-octadiene 1.9:1; [*N*-methylaniline] = 2 M. [f] Mixture of 1:1 *rac*/*meso* as estimated by NMR spectroscopy. [g] *N*-methylaniline/1,5-cyclooctadiene 1:3, 10 mol% **3**. Cy = cyclohexyl, TBDMS = tert-butyldimethylsilyl.

Table 3: Amine substrate scope using **3** as a precatalyst.



Entry	Amine	Alkene	*t* [h]	Product	Yield [%][a]
1			20[b,c]	 **12**	87
2			20[b,c]	 **13**	90
3			50[b,c]	 **14**	75[d,e,f]
4			37[b,g]	 **15**	92[e]
5			134[g,h]	 **16**	74[d,e,f]

[a] Yield of isolated product. [b] [*N*-methylaniline] = 1 M. [c] *N*-methylaniline/1-octene 1:1.5. [d] Isolated after derivatization as the *N*-tosyl amide. [e] A greater than 20:1 d.r. as estimated by NMR spectroscopy. [f] Isolated after derivatization as the *N*-toslylamide. [g] Amine/1-octene 1:3, 10 mol% **3**. [h] [piperidine] = 2 M, 165 °C. Ts = 4-toluenesulfonyl.

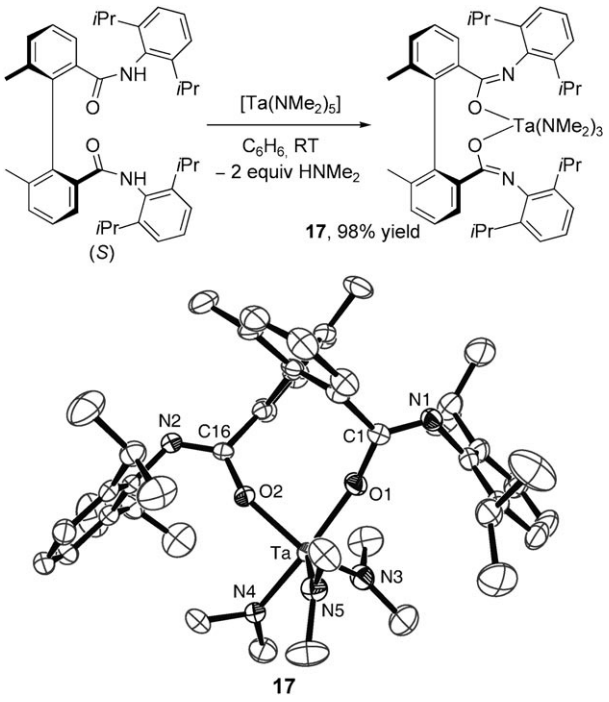
diamine diastereomers (**10**) in a 1:1 ratio. Alternatively, by using an excess of the unactivated internal diene 1,5-cyclooctene, this reaction results in step-wise addition to give the mono-alkylated product **11** selectively, leaving a C=C bond for additional functionalization.

Preliminary amine substrate scope investigations show that functionalized arylalkyl amines, dialkyl amines, and amine heterocycles all undergo catalytic α-alkylation (Table 3). Reacting 4-methoxy-*N*-methylaniline with terminal olefins delivers the corresponding *para*-methoxyphenyl (PMP) protected amines **12** and **13** in good yields.[11] The facile reactivity observed with these substrates provides a ready route for the synthesis of substituted primary amines, upon deprotection. In contrast to the work by Herzon and Hartwig,[4b] we observe exclusive alkylation at the benzylic position of *N*-benzyl methylamine, in accordance with relative C–H bond dissociation energies, to give a single diastereomeric product (**14**) in 75% yield after derivatization as the *N*-tosyl amide. Most importantly this class of catalysts can be used in the direct, diastereoselective alkylation of heterocycles such as 1,2,3,4-tetrahydroquinoline and piperidine. This is the first example of the 100% atom economic, catalytic α-alkylation of piperidine. The synthesis of substituted piperidines is typically achieved by multistep approaches.[12]

Chiral amidate precatalysts are known and we have previously used axially chiral diamines for the synthesis of tethered bis(amidate)–zirconium complexes for the highly enantioselective catalytic synthesis of amines by hydroamination.[13] In this case, the *cisoid* disposition of the oxygen atoms in the amidate in **1** suggests that axially chiral derivatives of diacids may be preferred for the synthesis of chiral, catalytically active tantalum complexes. The requisite biphenyl bis(amide) proligand is accessible by reacting the in situ formed 6,6′-dimethylbiphenyl-2,2′-dicarboxylic acid chloride[14] with 2,6-diisopropylaniline in the presence of NEt_3.[15]

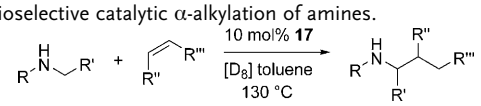
Precatalyst **17** was synthesized in excellent yield by a protonolysis reaction between [Ta$(NMe_2)_5$] and this C_2 symmetric tethered bis(amide) proligand (Scheme 4). The solid-state molecular structure of **17** reveals that this potentially tetradentate ligand adopts a bidentate alkoxyimine binding mode, to give a C_2 symmetric, pseudotrigonal bipyramidal tantlaum metal center. Solution phase NMR characterization data is also consistent with this C_2 symmetric binding mode, as the ^{13}C NMR spectrum shows one signal at $\delta = 159.92$ ppm for the carbonyl group, which is consistent with an alkoxyimine bonding mode.[16] Presumably, bidentate chelation (κ*O*, κ*O*′) is preferred over possible tetradentate (κ*O*, κ*N*, κ*O*′, κ*N*′) binding because of the chelate ring strain for this diacid derived proligand.

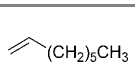
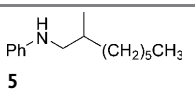
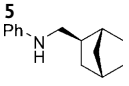
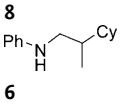
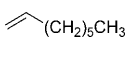
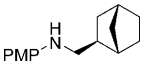
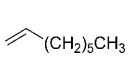
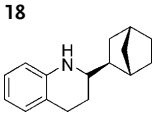
Chiral precatalyst **17** has been tested with a variety of alkene and amine substrates, and gives enantioenriched secondary amine products. The reaction of 1-octene with *N*-methylaniline (Table 4, entry 1), requires extended reaction times to proceed to completion and gives modest *ee* values. However, with



Scheme 4. Synthesis of chiral, enantiopure precatalyst and ORTEP diagram of the solid-state molecular structure of (±)-**17** with thermal ellipsoids depicted at 50% probability. All hydrogen atoms omitted for clarity. Selected bond distances [Å] and angles [°]: Ta–O1 2.015(2), Ta–O2 1.973(2), Ta–N3 1.926(3), Ta–N4 1.988(2), Ta–N5 1.956(2); O1-Ta-O2 85.21(10).

Table 4: Enantioselective catalytic α-alkylation of amines.



Entry	Amine	Alkene[a]	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1			68	 **5**	86	44
2			46	 **8**	80	61[d]
3			48	 **6**	92	43
4			24	 **18**	90	52[e]
5			192	 **19**	50	57[e]

[a] Amine/alkene 1:2. [b] Yield of isolated product. [c] The *ee* values were determined by HPLC analysis of benzamide derivative. [d] The *exo* configuration was confirmed by X-ray spectroscopy, but the absolute configuration was not established. [e] In analogy to entry 2.

a more sterically demanding alkene substrate, norbornene, catalysis in the presence of **17** for 46 hours results in an 80% yield (isolated) of diastereomerically pure product **8** in 61% *ee* (Table 4, entry 2). These preliminary asymmetric catalytic experiments show that alkenes with varying steric bulk give satisfactory reactivity and *ee* values (Table 4, entries 1–3) for this reaction. Importantly, different amines including a functionalized arylalkyl amine and an amine heterocycle can be used with this first generation chiral catalyst to generate amines **18** and **19** with 52% *ee* and 57% *ee*, respectively. The modest enantioselectivities obtained with this first example of a chiral tantalum complex for hydroaminoalkylation can be rationalized by the fact that only a bidentate binding mode is observed for this C_2 symmetric chiral ligand in both the solid state and solution phase. This less sterically demanding binding mode removes both the bulky N substituents and the enantiodetermining axially chiral biphenyl group from the reactive metal center. Thus, with our intimate understanding of the coordination chemistry in this new class of complexes, we anticipate that modification of this flexible ligand set can be used to build upon these first examples of asymmetric catalysis for the hydroaminoalkylation reaction.

In conclusion, the first examples of mono- and bis-(amidate)–tantalum complexes have been prepared and characterized. They show much promise for application in the catalytic hydroaminoalkylation of secondary amines. Spontaneous tantallaaziridine formation gives precatalyst **1**, a previously unobserved, yet proposed, catalytically active intermediate. Importantly, the substrate scope of the most reactive precatalyst includes terminal and internal alkenes (both activated and unactivated), some functional group tolerance in both the alkene and amine substrates, and even N-heterocycles such as piperidine can be used in this transformation. Preliminary results for an enantioselective process with several amine/olefin combinations show axially chiral biphenyl tethered bis(amidate)–tantalum complexes can be used to realize the first example of enantioenriched chiral amine synthesis by hydroaminoalkylation. Mechanistic investigations are currently underway to better understand the details of the β-hydrogen abstraction and the turnover-limiting step in the catalytic cycle. This mechanistic insight will guide modification of our new family of tantalum amidate complexes to enhance catalytic efficiency, improve substrate scope, and increase enantioselectivities in the synthesis of chiral amines by hydroaminoalkylation.

Experimental Section

All preparative scale reactions were conducted in oven dried glass ware with magnetic stirring using Schlenk-line techniques or a glove box under an atmosphere of dry N_2. Experiments on NMR tube scale were carried out in Teflon cap sealed NMR tubes (5 mm). Toluene, benzene, hexanes, and pentanes were purified by passage over an activated aluminum oxide column and degassed prior to use. [D_6]Benzene and [D_8]toluene were dried over 4 Å molecular sieves and degassed by three freeze-pump-thaw cycles. All commer-

cial amines and olefins for catalytic reactions were distilled under reduced pressure from CaH_2 and degassed by three freeze-pump-thaw cycles or sublimed in the case of solids. $[Ta(NMe_2)_5]$ was purchased from Strem and used as received.

General procedure for tantalum–amidate complex synthesis: Synthesis of **1** is given as a representative example: *N*-(2,6-dimethylphenyl)pivalamide (0.350 g, 1.71 mmol) was suspended in hexanes (2 mL). $[Ta(NMe_2)_5]$ (0.342 g, 0.853 mmol) was added as a solid and the solution was stirred overnight. The solvent was removed in vacuo and the resulting solid was recrystallized from hot hexanes at −35 °C, affording light yellow crystals. Typical yields in the range of 70–85 %.

General procedure for catalytic α-alkylation of amines: In a N_2 filled glove box the tantalum complex was placed in a small vial and the specified amount of (deuterated) solvent was added. The solution was transferred to an NMR tube equipped with a Teflon cap, and the olefin and the amine were added sequentially by means of a pipette. The NMR tube was closed, shaken, and the ^{1}H NMR spectrum was recorded. The NMR tube was placed in a preheated oil bath at the indicated temperature for the given time. After confirmation of conversion by means of ^{1}H NMR spectroscopy the crude reaction mixture was directly loaded onto a silica gel column and eluted using a mixture of hexanes/EtOAc/NEt_3 (100:1:1).

See the Supporting Information for additional experimental details, characterization data for compounds **1**–**20** and of the corresponding amide derivatives. CCDC 739133, 739134, 739135, 739136, and 739137 contain the supplementary crystallographic data for this paper (compounds **1**, **3**, **4**, **17**, **19**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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