Cooperative Catalysis

DOI: 10.1002/ange.201301849

An Efficient Approach to the Securinega Alkaloids Empowered by Cooperative N-Heterocyclic Carbene/Lewis Acid Catalysis**

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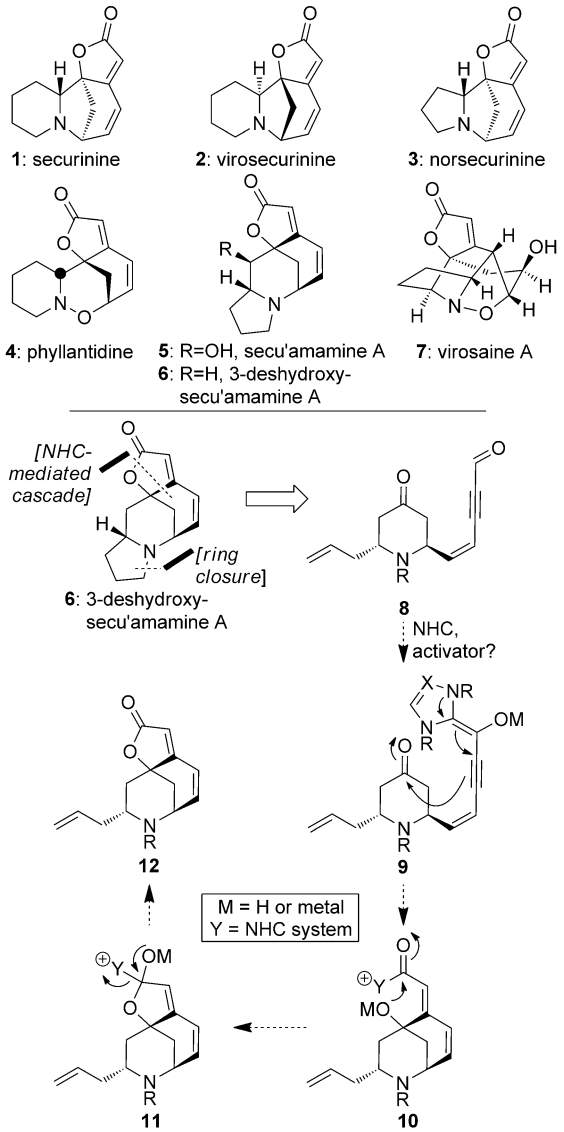
Dedicated to Professor Ronald Breslow on the occasion of his 82nd birthday

Plants of the *Euphorbiaceae* family are sources of several important collections of secondary metabolites, one being the securinega alkaloids (**1**–**5**[2] and **7**, Scheme 1).[1] These materials possess unique frameworks typically characterized by a bridged, tetracyclic substructure bearing a strained α,β,γ,δ-unsaturated lactone motif (as in **1**–**5**), though rearranged variants of such domains (such as in **7**)[3] also exist. They also display intriguing biological activity;[4] for instance, securinine (**1**), the most abundant member of the family, is a potent GABA antagonist. Given these attributes, it is unsurprising that the synthetic community has devoted significant attention to this collection of compounds,[5] particularly to the challenges posed by the key shared domains within **1**–**5**. Indeed, since the inaugural total synthesis of securinine (**1**) by Horii in 1966,[5a] several other successful and highly creative approaches for forging their fused bicyclic butenolide domains have been disclosed, efforts that include selenoxide eliminations,[5b,e,f,h,i,r] intramolecular Wittig olefinations,[5e,f,o,p,t–v] ring-closing metatheses,[5j–p,s,x] and alkylation of allylic bromides or mesylates.[5a,h,i–m,q,t–v,x] However, most of these strategies require multiple steps to execute, typically constituting the longest (and least efficient) portion of the overall route. Here, we disclose a new disconnection for this critical domain, one that uses a simple, acyclic starting material and a novel N-heterocyclic carbene (NHC)-catalyzed reaction[6,7] to forge the entire butenolide system in a single step. We highlight its utility through a concise and efficient synthesis of 3-deshydroxy-secu'amamine A (**6**, an analog of **5**[2] and a structural isomer of **1**) as well as the core framework of **1**–**3**, and indicate preliminary results of the components necessary for its successful application in other contexts.

Our generalized approach to quickly fashion the butenolide domains of the securinega class is shown in the lower half of Scheme 1, using target **6** for purposes of illustration. As indicated, we envisioned that this entire key motif could be accessed from an appropriate linear enynal precursor (**8**) through an intramolecular NHC-catalyzed homoenolate addition onto the lone ketone followed by lactonization.



Scheme 1. Structures of selected members of the securinega family of natural products and an approach for the rapid assembly of the core polycyclic domain of the targets.

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[**] We thank the NSF (CHE-0619638) for an X-ray diffractometer and Prof. Gerard Parkin and Aaron Sattler for performing our crystallographic analysis. Financial support was provided by Columbia University, the NSF (Predoctoral Fellowship to A.M.E.), and the Swiss Benevolent Society of New York (Predoctoral Fellowship to D.A.W.). S.A.S. is a Fellow of the Sloan Foundation and a Cottrell Scholar of the Research Corporation for Science Advancement.

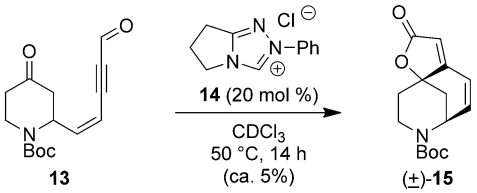
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301849.

These steps constitute a net [3+2]-addition of an ynal onto a ketone to afford what could be formally viewed as a hetero Pauson–Khand[8] product (**12**), without any need for the functional group interconversions, protecting groups, and/or redox adjustments typical of past approaches.

Despite its attractiveness on paper, there was little precedent indicating that such an approach would be successful in the laboratory. To the best of our knowledge, there are no examples of an ynal participating as a conventional nucleophile (i.e. not as a base) in a homoenolate setting; in fact, the few explorations utilizing ynals as substrates demonstrate instead that facile redox transfer through protonation of their derived homoenolates is the preferred reaction pathway.[9] Only one report detailing enal-derived homoenolates as nucleophiles toward unactivated ketones under NHC catalysis is known,[10] and in this case, good yields were realized only when non-enolizable ketones were deployed. Moreover, for our preferred substrates (i.e. **8**), we were concerned not only that the ynal motif itself might not be stable, but also that it might undergo non-productive intramolecular Michael addition with an enol or enolate derived from its ketone.[10] With additional conjugation to the ynal domain present, we were also cognizant of the possibility of further complications through homo-homoenolate reactivity. Nevertheless, we sought to test its viability, in that if such a transformation could be achieved, rapid access to the core of the securinega alkaloids would be obtained while concomitantly increasing the substrate scope and overall power of NHC catalysis.

Our explorations began with compound **13**, the corresponding diol of which is readily accessible in multi-gram quantities (see Supporting Information). Given its instability to bases such as Et_3N, we elected to start our explorations with amine-free conditions similar to those reported by Bode an co-workers for asymmetric Claisen rearrangements using NHC catalysts.[3c] Specifically, compound **13** was treated with NHC precatalyst **14**[11] in $CDCl_3$ and heated to 50 °C in an NMR tube. After 14 h, ^1H NMR analysis of the reaction mixture revealed ca. 5% conversion to a new compound. Following purification of the reaction mixture and subsequent X-ray crystallographic analysis, we confirmed that the new material was **15**, indicating that the desired cyclization had occurred [Eq. (1)]. Despite this initial hit, efforts to optimize the efficiency of the process through standard modifications (solvent, temperature, catalyst structure, and catalyst counterion) failed to provide isolated yields of **15** beyond 10%. All variants proved sluggish and, if the reaction was left for prolonged periods, significant decomposition was observed with no increase in the yield of **15**.

Given this state of affairs, recent reports by Scheidt and co-workers prompted us to consider using Lewis acid co-

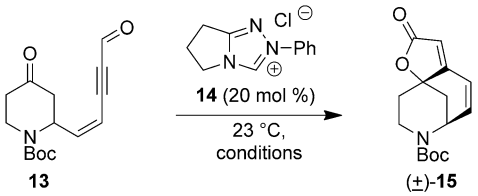


(1)

catalysts for our reaction.[12] We hoped that such an additive could: 1) activate the aldehyde for attack by the carbene, 2) activate the ketone for nucleophilic attack by the homoenolate, and 3) coordinate both the ketone and the presumed Breslow intermediate[13] (i.e. **9**, cf. Scheme 1) to organize the substrate for a productive reaction. However, all examples of using such co-catalysts in the literature have also required the presence of an exogenous base, a species seemingly incompatible with our starting material based on our initial explorations (see above). Our hope was that a Lewis acid such as $Ti(OiPr)_4$ might circumvent the need for an added base, hopefully providing enough activation and attendant basicity to promote the desired reaction.

Pleasingly, treatment of **13** with 2.0 equivalents of $Ti(OiPr)_4$ and 20 mol% of precatalyst **14** in CH_2Cl_2 at 23 °C for 12 h not only led to full consumption of the starting material, but also provided the desired tricyclic product in a markedly improved yield (37%, Table 1, entry 1). Highlights from our

Table 1: Initial optimization of the NHC/Lewis acid-catalyzed cyclization of **13**.



Entry	Base (15 mol%)	Lewis acid (equiv)	Solvent	Yield [%][a]
1	none	$Ti(OiPr)_4$ (2 equiv)	CH_2Cl_2	37
2	none	$Ti(OiPr)_4$ (1 equiv)	CH_2Cl_2	30
3	DBU	$Ti(OiPr)_4$ (2 equiv)	CH_2Cl_2	38
4	DBU	$Ti(OiPr)_4$ (1 equiv)	CH_2Cl_2	37
5	DBU	none	CH_2Cl_2	12

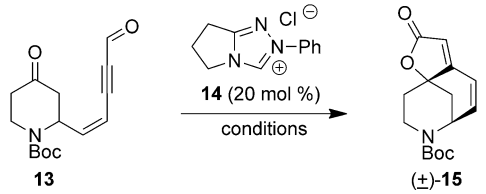
[a] Yields were determined by NMR analysis of the crude mixture using biphenyl as an internal standard.

extensive set of screening experiments to build on this new hit are presented in Table 1. Intriguingly, the inclusion of an amine base in substoichiometric quantities relative to the NHC precatalyst prior to addition of the starting material was tolerated and allowed the Lewis acid loading to be reduced to 1.0 equivalent, although no yield improvement was observed (Table 1, entry 4). Importantly, the use of base in the absence of the Lewis acid was much less efficient, with product formed in only 12% yield (Table 1, entry 5). Additionally, no other common Lewis acid was able to improve upon the results within Table 1. Indeed, many common Lewis acids known to promote NHC/Lewis acid cooperative catalysis, such as LiCl, $Mg(OtBu)_2$, $Sc(OTf)_3$, and $Mg(OTf)_2$, were completely ineffective in delivering product, while for titanium-based systems, the efficiency of the reaction was found to be highly sensitive to the ligand environment around the Ti^{IV} center. For example, exchange of the isopropoxide ligands with *tert*-butoxide led to a decrease in yield while replacement of a single isopropoxide with chloride failed to deliver any detectable amount of product (see the Supporting Informa-

tion for a tabulation of some of these results). As such, $Ti(OiPr)_4$ was used for the remainder of our studies.[14]

The key to the next level of improvement resided in our observation during these optimization studies that crude mass recoveries were consistently low and consisted only of product after simple filtration through a small pad of silica gel. We ultimately learned that while the product itself was stable to $Ti(OiPr)_4$ and the overall reaction conditions, the starting material underwent Lewis acid-mediated decomposition. A concentration screen (Table 2) then suggested that

Table 2: Concentration screen for the conversion of **13** to **15**.[a]



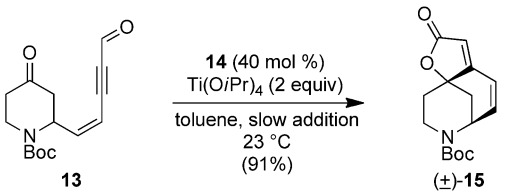
Entry	Conc. [M]	Solvent	Yield [%][b]
1	0.1	CH_2Cl_2	25
2	0.05	CH_2Cl_2	38
3	0.01	CH_2Cl_2	49
4	0.005	CH_2Cl_2	41[c]

[a] All reactions were conducted at 23 °C with 20 mol% **14**, 15 mol% DBU, and 1 equiv $Ti(OiPr)_4$ for 18 h. [b] Yields were determined by NMR analysis of the crude mixture using biphenyl as an internal standard. [c] At 97% conversion.

the decomposition was likely intermolecular in nature, with a concentration of 0.01M proving optimal if all the starting material was initially present with the full amount of the Lewis acid (Table 2, entry 3). As an alternative method, we also found that the starting material could be introduced to the reaction via slow addition over the course of 4 h; although a 49% yield was obtained in both cases, the final reaction concentration could be increased to 0.04M with the latter protocol.[16]

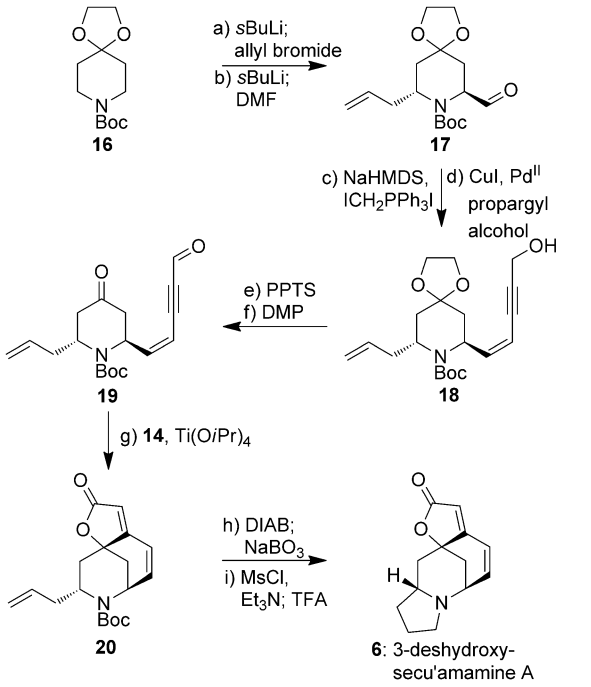
Given the marked improvement of our slow addition protocol, we elected to re-examine the choice of reaction solvent. To our delight, changing the solvent from CH_2Cl_2 to toluene in this procedure proved beneficial. Further screening of the catalyst loading provided a superior protocol: slow addition of starting material **13** as a toluene solution to a suspension of 0.4 equivalents of **14** and 2.0 equivalents of $Ti(OiPr)_4$ in toluene to reach a final concentration of 0.03M. As shown in Equation (2), this procedure led to product **15** in 91% isolated yield (0.2 mmol scale reaction). Importantly, the use of catalyst loadings higher or lower than 20 mol% with CH_2Cl_2 as solvent provided an inferior yield. Though the reason for this yield improvement is not fully understood, the near insolubility of precatalyst **14** in toluene[17] could further reduce the concentration of reactive species in solution, resulting in an improved yield.

With this success in hand, we then embarked on a synthesis of natural product analog 3-deshydroxy-secu'amamine A (**6**) to determine if additional substituents on the core piperidone



(2)

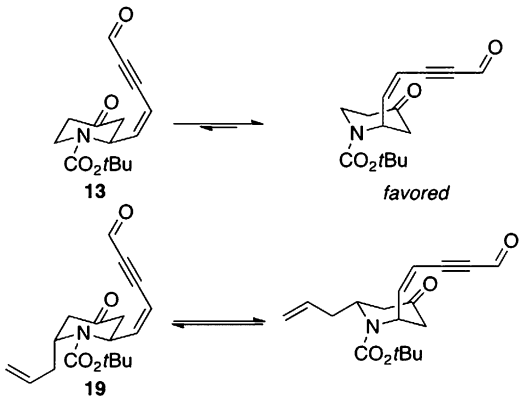
ring system would be tolerated in our critical NHC-induced cascade assembly of the butenolide domain. Thus, as shown in Scheme 2, Boc- and ketal-protected piperidone **16** was subjected to sequential deprotonation/alkylation[18] to establish the 2,6-*trans*-stereochemistry of the piperidine ring within **17** in good overall stereoselectivity (> 8:1). Installation of the requisite enyne moiety in **18** proceeded through a two-step protocol involving Stork–Wittig olefination[19] of the aldehyde



Scheme 2. Synthesis of 6-deshydroxy-secu'amamine A (**6**): a) *s*BuLi (1.4M in cyclohexane, 1.5 equiv), TMEDA (1.6 equiv), Et_2O, −78→−40 °C, 1 h; CuCN·2LiCl (1.5 equiv), THF, −78 °C, then allyl bromide (5.0 equiv), −78→23 °C, 12 h, 65% (unoptimized); b) *s*BuLi (1.4M in cyclohexane, 1.8 equiv), TMEDA (2.2 equiv), Et_2O, −78→−40 °C, 1 h, then DMF (10 equiv), −78→−40 °C, 1.5 h, 60% (unoptimized); c) NaHMDS (1.0M in THF, 1.2 equiv), ICH_2PPh_3I (1.25 equiv), THF/HMPA (10:1), −78 °C, 1 h, 80%; d) CuI (14 mol%), $PdCl_2(NCPh)_2$ (7 mol%), propargyl alcohol (3 equiv) THF/piperidine (2:1), 23 °C, 24 h, 86%; e) PPTS (1.5 equiv), *t*BuOH/H_2O (5:1), 75 °C, 15 h, 78%; f) Dess–Martin periodinane (1.25 equiv), CH_2Cl_2, 23 °C, 1 h, >98%; g) **14** (40 mol%), $Ti(OiPr)_4$ (2 equiv), toluene, 50 °C, slow addition over 8 h, 8 h additional stirring, 47%; h) DIAB (5.0 equiv), THF, −25→10 °C over 2 h; aq. $NaBO_3$, 23 °C, 4.5 h, 72%; i) MsCl (2.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 12 h, then TFA, 0 °C, 1 h, 92%. DIAB = disiamylborane, DMF = dimethylformamide, HMDS = hexamethyldisilazide, HMPA = hexamethylphosphoramide, Ms = methanesulfonyl, PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

and subsequent Sonogashira coupling in 69% overall yield. Importantly, no epimerization of the aldehyde was observed during the olefination step (see Supporting Information for full details). Next, deprotection of the ketal with PPTS in *t*BuOH/H_2O (5:1) at 75°C furnished the desired ketone in 78% yield without any observable alkene isomerization, while subsequent oxidation of the primary alcohol with Dess–Martin periodinane[20] furnished enynal **19** in excellent yield (>98%), setting the stage for our key cyclization event.

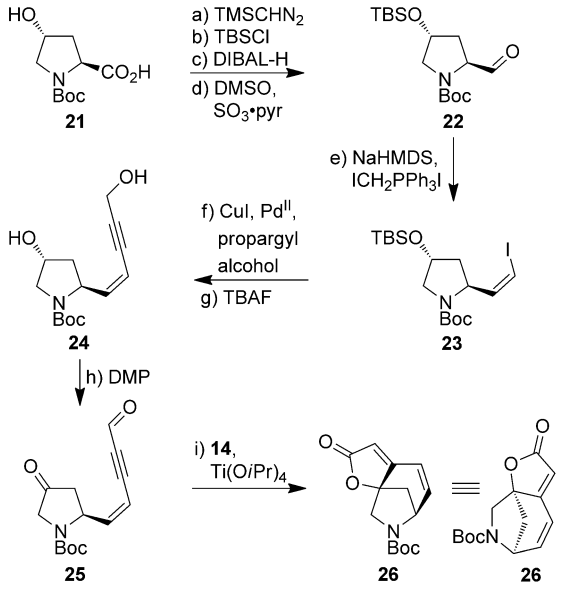
Pleasingly, slow addition of a solution of **19** to a suspension of $Ti(OiPr)_4$ and precatalyst **14** in toluene using our previously optimized conditions (0.03 M) was effective in delivering the desired tricyclic compound (**20**); however, the yield of **20** (28%) was much lower than in our previous model study. Fortunately, lowering the final concentration to 0.02 M led to an increase in yield to 35%. The diminished yields for **20** relative to our model (**15**) suggests that substrate **13** may possess a conformational bias that facilitates the reaction given that carbamate-protected piperidines generally prefer an axial orientation of C2 substituents when monosubstituted.[18] In **19**, however, the presence of 2,6-*trans*-disubstitution likely induces a conformational equilibrium in which the desired enynal only resides in the axial orientation intermittently (Scheme 3). In line with that supposition, heating of the



Scheme 3. Important conformational dynamics in **13** and **19** leading to observed differences in yield of the key reaction.

reaction mixture to 50°C during the slow addition process provided a notable yield increase to 47%. From here, butenolide **20** was thus taken forward with a chemoselective hydroboration/oxidation sequence[21] furnishing the desired primary alcohol in 72% yield, with **6** then accessed in 92% yield by a one-pot methane sulfonate ester formation/*N*-Boc deprotection/cyclization sequence.

As a final study, we wanted to examine the ability of this NHC/Lewis acid reaction to forge bridging butenolide cores within [3.2.1]-bicycles as well, a motif found within a large number of securinega alkaloids such as securinine (**1**) and norsecurinine (**3**). Thus, we prepared compound **25** through the route delineated in Scheme 4 (drawing from many of the lessons learned in the context of Scheme 2) and, to our delight, found that our protocol could deliver the desired [3.2.1]-bicyclic framework of **26** in 31% yield when heated to



Scheme 4. Synthesis and NHC-induced cyclization of **25** to deliver the [3.2.1]-bicyclic core (**26**) found in various securinega alkaloids: a) $TMSCHN_2$ (2.0 M in toluene, 1.1 equiv), THF/MeOH (10:1) −78→23°C over 1 h, 99%; b) TBSCl (1.3 equiv), imidazole (1.8 equiv), CH_2Cl_2, 23°C, 12 h, 98% over 2 steps); c) DIBAL-H (1.0 M in toluene, 2.5 equiv), THF, −78°C, 45 min, then 23°C, 10 min, 98%; d) SO_3·pyr (3.0 equiv), Et_3N (4.0 equiv), DMSO/CH_2Cl_2 (2:1), 0→23°C, 45 min, 90–97%; e) NaHMDS (1.0 M in THF, 1.2 equiv), ICH_2PPh_3I (1.25 equiv), THF/HMPA (10:1), −78→−40°C, 1 h, 50%; f) CuI (14 mol%), $PdCl_2(NCPh)_2$ (7 mol%), propargyl alcohol (3 equiv) THF/piperidine (2:1), 23°C, 24 h, 78%; g) TBAF (1.0 M in THF, 1.5 equiv), THF, 23°C, 14 h, 94%; h) Dess–Martin periodinane (2.5 equiv), CH_2Cl_2, 23°C, 1.5 h, >95%; i) **14** (40 mol%), $Ti(OiPr)_4$ (2 equiv), toluene, slow addition over 4 h, 50°C, 12 h, 31%. TMS = trimethylsilyl, DIBAL-H = diisobutylaluminum hydride.

50°C.[24] This outcome highlights that several variants of the butenolide core found within the family can be accessed using this general approach in a number of different contexts. At present, work to apply these reactions to fully functionalized materials capable of accessing natural products is underway, as is the exploration of the full substrate scope of this reaction. Immediately clear is that the conformational bias provided by the *N*-Boc protecting group within **13** is essential for delivering high yields, as its fully carbogenic congener is much less efficient. Furthermore, the alkene moiety appears to provide a further benefit in restricting the degrees of rotational freedom available to the side chain. Thus, it appears that this reaction manifold is highly sensitive to the conformation adopted by the various substrates, and those substrates that are suitably oriented to facilitate the desired reaction through either conformational locking or restriction of rotational degrees of freedom have a greater chance for success.

In conclusion, we have developed and applied a novel and efficient NHC/$Ti(OiPr)_4$ cascade reaction to the synthesis of the tricyclic framework of the securinega alkaloids. This reaction has enabled access to **6** and compound **26** in only 9 linear steps from commercial materials, a length which compares favorably to past approaches,[22] and has demonstrated the viability of ynal-derived homoenolates as nucle-

ophiles in an intramolecular setting. Noteworthy is that the synthesis of **6** outlined in this work is redox economic,[23] enabled by our key NHC/Lewis acid transformation. Thus, we anticipate that these studies will provide opportunities for the development of further NHC-catalyzed reactions using ynals as nucleophilic homoenolate precursors,[25] as well as efficient syntheses of natural product members of the securinega family.

Received: March 5, 2013
Published online: April 22, 2013

Keywords: alkaloid · cascade reaction · natural product · *N*-heterocyclic carbene · securinega

[1] For a summary of the early isolations of various *Securinega* alkaloids, see: "The Securinega Alkaloids": V. Snieckus in *The Alkaloids*, *Vol. 14* (Ed.: R. H. F. Manske), **1975**, pp. 425 – 506. Intriguingly, compounds **1** and **2** are enantiomeric and have been isolated as single antipodes from their producing organisms. For an interesting review on enantiomeric natural products, see: J. M. Finefield, D. H. Sherman, M. Kreitman, R. M. Williams, *Angew. Chem.* **2012**, *124*, 4886 – 4920; *Angew. Chem. Int. Ed.* **2012**, *51*, 4802 – 4836.

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