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Alkali Base-Initiated Michael Addition/ Alkyne Carbocyclization Cascades

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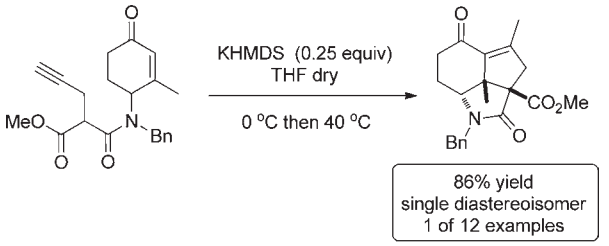

A new cascade reaction involving an intramolecular Michael addition followed by an alkyne carbocyclization is presented. The reaction is promoted by a substoichiometric amount of KHMDS and represents one of the rare examples where the carbocyclization of an unactivated alkyne is mediated by an alkali metal base, under mild conditions. The reaction allows the generation of functionally dense, stereochemically defined, tricyclic structures possessing three adjacent stereocenters in good yields and with high stereoselectivity.

Cascade reactions are valuable tools in the hands of organic chemists, allowing the generation of molecular complexity from readily available starting materials. During a cascade process, several new carbon−carbon bonds and stereogenic centers can be created in one pot in a highly controlled fashion, thus facilitating the execution of short and efficient reaction routes.[1] The development of new catalyzed cascade sequences represents an ultimate goal, in terms of economy of resources, time, and reduction of waste generation. Our group has developed several catalytic cascade sequences involving activation of alkyne functionalities toward nucleophilic addition via the use of appropriate transition metal ions such as copper[2] or gold[3] complexes.

We envisaged that compounds like structure **1** (Scheme 1), bearing two electrophilic centers and two nucleophilic centers, would represent an ideal substrate for a cascade process involving an initial Michael addition step, followed by a carbocyclization of the newly formed ketone-enolate onto the pendant alkyne functionality, as illustrated in Scheme 1. We planned to realize this transformation by means of a multicatalytic system comprising a combination of a Brønsted basic/secondary amine catalyst to promote the Michael addition step and a transition metal catalyst to promote the nucleophilic addition onto the alkyne functionality.

In order to test our hypothesis, we prepared malonamate derivative **4a** (Table 1), and we decided to first study the Michael addition step using a series of organic/inorganic catalysts. To our surprise, when compound **4a** was treated with inorganic bases such as KH, KHMDS, or NaHMDS, the main product isolated from the reaction mixture was not the expected Michael adduct **5** but compound **6a**

(1) For reviews on cascade reactions see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006; p 672. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619–1665. and 2143–2173.

(2) (a) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140–9141. (b) Wang, H.-F.; Yang, T.; Xu, P.-F.; Dixon, D. J. *Chem. Commun.* **2009**, 3916–3918. (c) Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D. J. *Chem. Commun.* **2008**, 2923–2925.

(3) (a) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071. (b) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797. (c) Barber, D. M.; Sanganee, H.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 4379–4381.

(4) For reviews on carbocyclization to carbon-carbon multiple bonds, see: (a) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366–2447. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662.

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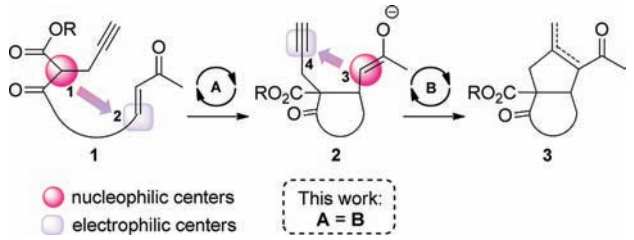
Scheme 1. Concept for the Michael Addition/Alkyne Carbocyclization Cascade



(Table 1), derived from an initial intramolecular Michael addition followed by an alkyne carbocyclization and an isomerization step.

Although numerous examples of carbocyclizations of nucleophiles onto unactivated alkynes are known,[4] less common are those mediated by alkali metal bases, especially under catalytic conditions.[5]

Herein, we report the discovery, optimization and the substrate scope of this new catalyzed cascade reaction, promoted by alkali metal bases.

When a solution of precursor **4a** in tetrahydrofuran was treated with a stoichiometric amount of potassium bis-(trimethylsilyl)amide (KHMDS) (15% w/w solution in toluene),[6] the only product present in the reaction mixture was tricycle **6a**, which was isolated in 43% yield (entry 1, Table 1) as a single diastereoisomer.[7]

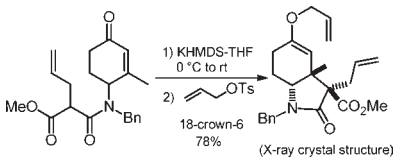
The reaction outcome proved similar when tetrahydrofuran was replaced with toluene, but a longer reaction time was required (entry 2, Table 1). When 1,4-dioxane was used as solvent, a comparable result to the use of tetrahydrofuran was obtained (entry 3, Table 1).

We hypothesized that the low yield obtained in entries 1–3 was due to partial decomposition under the reaction conditions, rather than to lack of reactivity (no starting material **4a** or Michael adduct **5** were observed by NMR analysis of the crude reaction mixture for entries 1–3 in Table 1). When sodium and potassium bis-(trimethylsilyl)amides were used

(5) (a) Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1953**, 3052–3059. (b) Kitagawa, O.; Suzuki, T.; Fujiwara, H.; Fujita, M.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 4585–4588. (c) Gao, K.; Wu, J. *Org. Lett.* **2008**, *10*, 2251–2254. (d) Dumez, E.; Durand, A.-C.; Guillaume, M.; Roger, P.-Y.; Faure, R.; Pons, J.-M.; Herbette, G.; Dulcère, J.-P.; Bonne, D.; Rodriguez, J. *Chem.—Eur. J* **2009**, *15*, 12470–12488. (e) Guillaume, M.; Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Synlett* **2002**, *11*, 1883–1885.

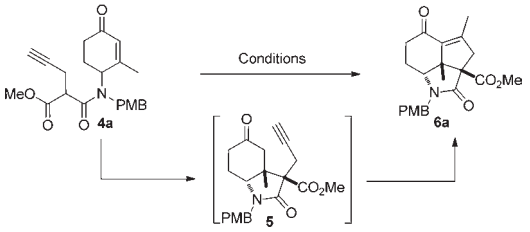
(6) Several different batches of KHMDS solutions were tested. KHMDS solutions in THF and toluene from Aldrich, Alfa Aesar, and Acros were tested, and in all cases, comparable results were obtained.

(7) The stereochemistry of **6a** was assigned by analogy to the product of the intramolecular Michael addition/enolate alkylation reaction shown below, which was established via single crystal X-ray analysis.



For details, see: Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132–5135.

Table 1. Optimization of the Reaction Conditions



entry	base	solvent	temp (°C)/ time	concn (M)	yield (%)[a]
1	KHMDS (1.00 equiv)	THF	0 °C/10 min 20 °C/2 h	0.03	43
2	KHMDS (1.00 equiv)	toluene	0 °C/10 min 20 °C/24 h	0.03	44
3	KHMDS (1.00 equiv)	dioxane	0 °C/10 min 20 °C/2.5 h	0.03	43
4	*t*-BuOK (0.50 equiv)	THF	0 °C/45 min 40 °C/4 h	0.03	–[b]
5	NaHMDS (0.50 equiv)	THF	0 °C/45 min 40 °C/4 h	0.03	59
6	KHMDS (0.50 equiv)	THF	0 °C/45 min 40 °C/4 h	0.03	51
7	KH (0.5 equiv)	THF	0 °C/45 min 40 °C/20 h	0.03	81
8	LHMDS (0.50 equiv)	THF	0 °C/45 min 40 °C/72 h	0.03	–[b]
9	KHMDS (0.25 equiv)	THF	0 °C/45 min 40 °C/4 h	0.03	79
10	KHMDS (0.25 equiv)	THF	0 °C/45 min 20 °C/9.5 h	0.03	–[c]

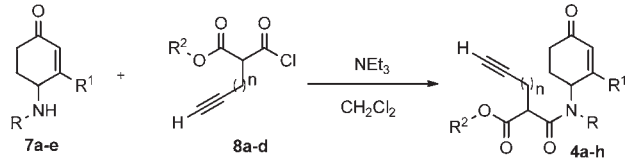
[a] Isolated yield. [b] Only the Michael adduct intermediate was isolated. [c] An inseparable mixture of Michael adduct **5** and **6** was obtained in a 0.84:1.00 ratio as determined by ^{1}H NMR analysis of the crude reaction mixture.

in substoichiometric amount (0.5 equiv), the reaction yield was increased respectively to 59 and 51% (entries 5 and 6, Table 1), while *t*-BuOK and LHMDS were unable to promote the cascade process and yielded Michael adduct **5** (entry 4 and 8, Table 1).[8] Further reduction of the amount of base to 0.25 equiv led to a satisfactory 79% yield of the desired tricycle **6a** (entry 9, Table 1). Decrease of the reaction temperature from 40 to 20 °C did not result in a full consumption of the intermediate Michael adduct **5**. Similarly, a decrease of the amount of KHMDS from 0.25 to 0.10 equiv resulted in incomplete consumption of intermediate **5** after heating in THF at 40 °C for 24 h. We therefore identified optimal reaction conditions as those reported in entry 9 in Table 1: initially, a solution of precursor **4** was treated with KHMDS at 0 °C and stirred at this temperature for 45 min, in order to let the Michael addition take place. Subsequently, the reaction mixture was transferred to a preheated oil bath at 40 °C and stirred until all intermediate **5** was converted to product **6**. It should be noted that a rigorous exclusion of air

(8) At present, the effect of the nature of the alkali base on the reaction outcome remains unclear. However, when KH is used as promoter, turnover is observed, therefore suggesting that enolate **13** (c.f. Scheme 3) is competent as the reaction promoter.

and moisture was required in order to obtain acceptable results, and the use of Schlenk line techniques was found ideal for guaranteeing the reproducibility of the reaction.

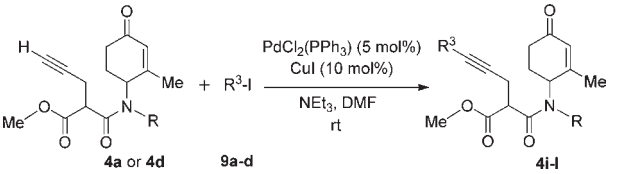
Table 2. Preparation of Cascade Precursors **4a**–**4h**

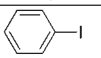
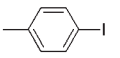


entry	7	8	4 yield (%)
1	**7a**, R = PMB, R^1 = Me	**8a**, R^2 = Me, n = 1	**4a**, 74
2	**7b**, R = Bn, R^1 = Me	**8a**, R^2 = Me, n = 1	**4b**, 64
3	**7c**, R = $CH_2CH{=}CH_2$, R^1 = Me	**8a**, R^2 = Me, n = 1	**4c**, 63
4	**7d**, R = $CH_2CH(OMe)_2$, R^1 = Me	**8a**, R^2 = Me, n = 1	**4d**, 79
5	**7e**, R = PMB, R^1 = n-pentyl	**8a**, R^2 = Me, n = 1	**4e**, 86
6	**7a**, R = PMB, R^1 = Me	**8b**, R^2 = t-Bu, n = 1	**4f**, 70
7	**7a**, R = PMB, R^1 = Me	**8c**, R^2 = Bn, n = 1	**4g**, 84
8	**7a**, R = PMB, R^1 = Me	**8d**, R^2 = Me, n = 2	**4h**, 81

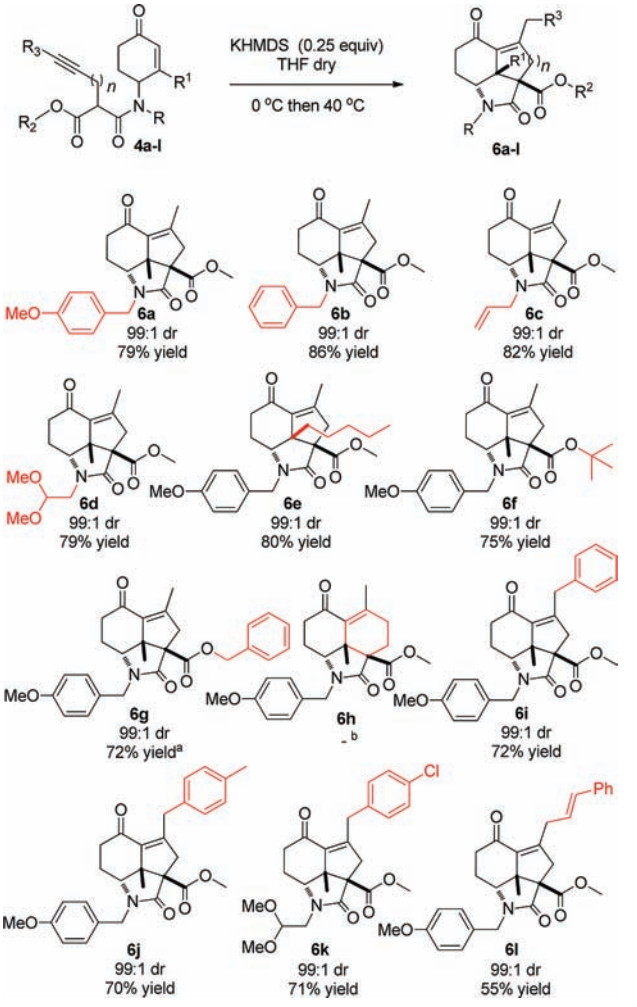
Once the optimal reaction conditions were identified, the reaction scope was surveyed. For this purpose, a series of precursors **4a**–**4h** were readily prepared using standard amide coupling of amines **7a**–**e** with acid chlorides **8a**–**d**, as detailed in Table 2. Further precursors **4i**–**4l**, bearing an internal acetylenic function, were prepared via Sonogashira coupling of **4a** or **4d** with iodo-derivatives **9a**–**9d**, as shown in Table 3. With 12 substrates **4a**–**4l**, presenting five diversification points (R–R^3 and n) in hand, the carbocyclization cascade was tested using optimal conditions, and the results are presented in Scheme 2. Substitution on the amine was well tolerated, and various groups could be introduced in this position without affecting the diastereoselectivity or yield of the cyclization process: tricyclic compounds **6a**–**6d** were obtained in good yields ranging from 79 to 86%, and all of them were obtained as single diastereoisomers. Substitution on the cyclohexene ring was investigated through introduction of a n-pentyl chain on the β-carbon (R^1 group in compound **4e**). Pleasingly, also in this case the expected product **6e** was obtained in good yield upon exposure to the optimized reaction conditions. We then investigated substitution on the ester group and prepared substrates incorporating a t-butyl ester and a benzyl ester (substrates **4f** and **4g**). Steric hindrance on the ester group was found to have no effect on the diastereoselectivity, and tricyclic products **6f** and **6g** were isolated in respectively 75 and 72% yield as single diastereoisomers.

Table 3. Preparation of Cascade Precursors **4i**–**4l**



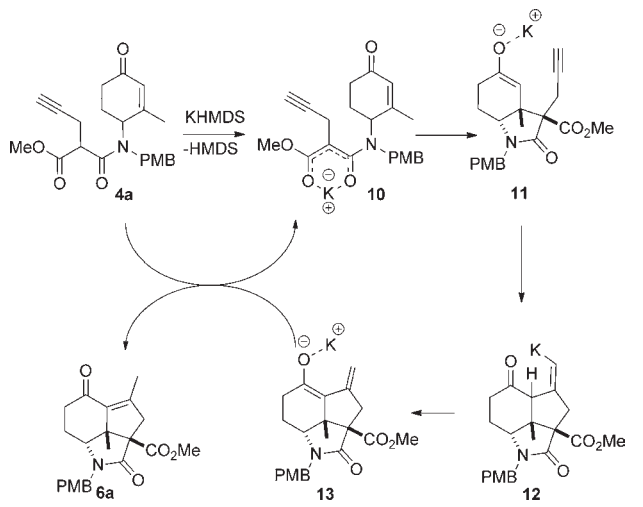
entry	4a / 4d	9	4i-l yield (%)
1	**4a**	**9a**, 	**4i**, 81
2	**4a**	**9b**, 	**4j**, 80
3	**4d**	**9c**, 	**4k**, 71
4	**4a**	**9d**, 	**4l**, 76

Scheme 2. Scope of the Reaction



[a] The reaction was performed with 0.5 equiv of KHMDS.
[b] Only the intermediate Michael adduct was isolated.

Scheme 3. Plausible Mechanistic Hypothesis



Notably, non-terminal alkynes were also effective substrates for the cyclization. Substituted aromatic groups could be introduced at the terminal acetylenic position: compounds **4i**–**4k** were successfully cyclized with good yield, independently of the substitution on the aromatic ring.

Precursors **4j** and **4k**, bearing respectively a *p*-Me and a *p*-Cl substituted aromatic ring were both cyclized with comparable yield (70 and 71%). Also, alkene groups could be introduced at the terminal acetylenic position via Sonogashira coupling: **4a** was coupled with (*E*)-(2-iodovinyl)benzene (**9d**) to give **4l**, which was successfully converted to tricycle **6l** in 55% yield when treated under optimized reaction conditions. Interestingly, for compounds bearing an internal acetylene group, a single regioisomer bearing the newly formed double bond in conjugation with the ketone, not the arene or alkene, was obtained.

The fact that for all examples reported in Scheme 2 the final products possess a conjugated enone suggests that the preferential formation a stable conjugated system is necessary for the reaction to occur. Although a detailed mechanistic investigation has not been carried out, we hypothesize the scenario illustrated in Scheme 3, where the alkali base acts as a promoter, initiating the cascade process via an initial and irreversible deprotonation of the C_α–H of malonamate **4a**. A subsequent Michael addition of the potassium enolate with the cyclohexenone generates a second enolate **11** that undergoes carbocyclization with the pendant alkyne group to give **12**. A final series of proton transfer steps leads to the formation of extended enolate **13**. A final protonation of **13** from a molecule of starting material results in product **6a** and the regeneration of malonamate enolate **10**.

In summary, we have discovered and developed a new cascade process involving a Michael addition/alkyne carbocyclization cascade initiated using substoichiometric quantities of alkali metal base. The reaction takes place under mild conditions and gives access to stereochemically defined, tricyclic structures in good yields and high stereoselectivity. Further investigation of this transformation, as well as application to total synthesis, is currently under investigation in our laboratories.

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Supporting Information Available. Experimental procedures and spectral data for compounds **4a**–**4l**, **5a**, **6a**–**6g**, **6i**–**6l**, **7a**–**7e**, and all intermediates required for their preparation, and experimental procedures for **8a**–**8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.