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Microwave-Assisted Tandem Cross Metathesis Intramolecular Aza-Michael Reaction: An Easy Entry to Cyclic β-Amino Carbonyl Derivatives

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Tandem or cascade processes[1] have emerged as a powerful tool to perform several chemical reactions in a single process, increasing molecular complexity in only one operation and thus avoiding the handling and isolation of intermediates. The design of a tandem process is not generally obvious requiring two criteria: (1) compatibility of reagents with each product formed in any single reaction and (2) high conversion in each single reaction to obtain a high-yielding sequence. Among all reagents used in tandem processes, it is worth mentioning the use of ruthenium alkylidene complexes.[2] Their development in terms of stability and commercial availability has led chemists to access a wide range of synthetic applications and have extended their usefulness.

In this sense, Grubbs et al.[3] reported a very elegant straightforward synthesis of (*R*)-(−)-muscone via one-pot, three-component RCM-transfer dehydrogenation−hydrogenation catalyzed by a single Ru source. Several successful examples of tandem processes have been described since then, involving a RCM−isomerization sequence,[4] a one-pot three-component tandem RCM−Diels−Alder reaction,[5] a tandem RCM−Kharasch addition,[6] a RCM−dihydroxylation sequence,[7] a ROM−RCM reaction,[8] a CM−allylic alcohol isomerization process,[9] a tandem enyne metathesis/Claisen rearrangement,[10] or a tandem enyne metathesis followed by a cyclopropanation of the newly formed exo-cyclic double bond.[11]

To the best of our knowledge, no example of a CM−aza-Michael tandem process has been described, and encouraged by recent advances in tandem processes we decided to explore such a sequence. The aza-Michael reaction leads to the creation of β-amino carbonyl units, which are very important structures present in a large number of natural products and pharmaceutical ingredients. Although many examples of aza-Michael addition of *N*-protected amines or their synthetic equivalents to α,β-unsaturated carbonyl compounds have been described in its intermolecular variant, very little is known about its intramolecular counterpart. All these reasons prompted us to explore this tandem protocol that makes a rapid access to Cbz-protected β-homoproline and β-pipecolic acid derivatives in only one step, possible using readily available starting materials (Scheme 1).

Initial screening reactions were conducted using carbamates as nitrogen nucleophiles. Thus, the Cbz-protected starting amines **2** were obtained from the corresponding commercially available nitrile by $LiAlH_4$ reduction and nitrogen protection. A model reaction between methyl vinyl ketone **1a** and amine **2a** was used to optimize the reaction conditions. In the presence of second generation Grubbs catalyst **I** (10 mol %) in dichloromethane (DCM) under reflux, the only formed product after 5 h was **3a**, the corresponding cross-coupled product between both methyl vinyl ketone **1a** and **2a** in 45% yield. The corresponding tandem process product **4a** was not detected (Table 1, entry 1).

Scheme 1. Synthetic Strategy for the Preparation of β-Amino Carbonyl Units

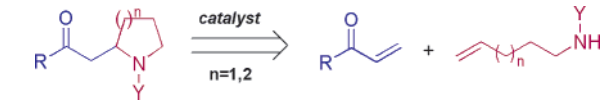
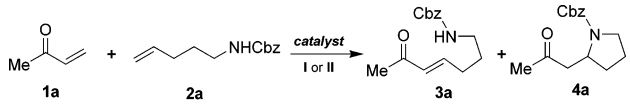


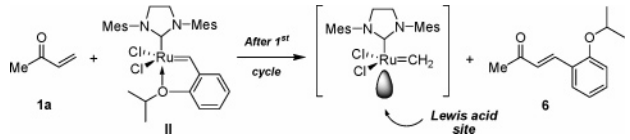
Table 1. Optimization Conditions of the Tandem Protocol



$Cl_2(IMes)(PCy_3)Ru=CHPh$ (**I**)
$Cl_2(IMes)Ru=CH$ (*o*-*i*-$PrOC_6H_4$)(**II**)

entry	catalyst	conditions	% **3a**	% **4a**	additive
1	**I**	DCM/Δ/5 h	45		none
2	**II**	DCM/Δ/5 h	71	3	none
3	**II**	toluene/Δ/5 h	35	21	none
4	**II**	DCM/45 °C/4d		99	$BF_3{\cdot}OEt_2$
5	**II**	DCM/100 °C μwave/20 min		96	$BF_3{\cdot}OEt_2$

Scheme 2. Reaction of Ruthenium Ligand with Enone **1a**



The reduction of catalyst loading (5 mol %) and longer reaction times did not produce any significant improvement in the process. We then decided to check Hoveyda−Grubbs catalyst **II** since it has been described to facilitate cross-coupling reactions between olefins bearing EWG and terminal olefins.[12] Using the aforementioned conditions, the use of catalyst **II** provided 71% of the CM product together with a small amount of the tandem adduct (3%) (Table 1, entry 2). We next explored the influence of the temperature, and thus the reaction was carried out in toluene under reflux giving rise to 21% of the tandem adduct and 35% of the CM product (Table 1, entry 3). This result led us to consider the possibility that catalyst **II** would be acting as a weak Lewis acid through its axial coordination site (oxygen ligand). Once the first catalytic cycle is completed, the styrene moiety leaves the metal coordination sphere, and the ruthenium acts as a Lewis acid through its empty *d* orbital. This assumption was supported by the fact that compound **6** was isolated as a byproduct in the CM reaction (Scheme 2). At the same time it might explain why catalyst **II** works better than **I** in the tandem protocol, since the axial phosphine ligand remains bonded to the ruthenium in catalyst **I**, avoiding the activation of the aza-Michael step.

At this point, we decided to evaluate the use of some additives to activate the cyclization step. It is well-known that carbamates are weak nucleophiles in aza-Michael reactions, and either a basic[13]

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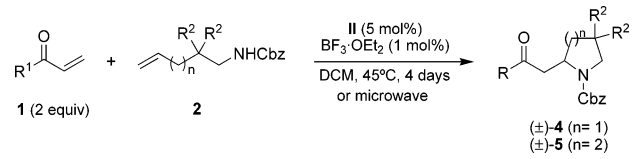
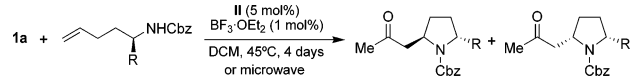
Table 2. Scope of the Tandem Protocol



1	2	R^1	*n*	R^2	(±)-4,5	% yield[a]
1a	**2a**	Me	1	H	**4a**	99 (96)
1a	**2b**	Me	2	H	**5a**	82 (93)
1b	**2a**	*n*-Pr	1	H	**4b**	73 (65)
1b	**2b**	*n*-Pr	2	H	**5b**	79 (72)
1c	**2a**	*n*-Pn	1	H	**4c**	81 (70)
1c	**2b**	*n*-Pn	2	H	**5c**	83 (61)
1a	**2c**	Me	1	F	**4d**	60 (55)

[a] In brackets are the yields obtained when the reaction was performed under microwave irradiation.

Table 3. Tandem Protocol with Substituted Amines **7**



7	R	8,9	% yield (8/9)[a,b]	% yield (8/9)[a,c] (μwave)
a	*i*-Pr	**a**	97 (3/1)	81 (1/4)
b	Ph	**b**	98 (6/1)	86 (1/2)
c	PMP[d]	**c**	78 (4/1)	97 (1/2)
d	CF_3	**d**	76 (5/1)	97 (1/3)

[a] Diastereomeric ratios were determined by GC-MS. [b] Thermal reaction. [c] Microwave irradiation reaction. [d] PMP = 4-MeO−C_6H_4.

or acidic[14] activation is needed. It has been previously described that boron compounds efficiently promote CM reactions of enones in the presence of catalyst **II**.[15] Furthermore, these substrates have also been employed in the intermolecular aza-Michael addition of carbamates.[16] Since $BF_3{\cdot}OEt_2$ has shown its compatibility with both types of processes, we decided to use it as the additive. We performed the tandem protocol with catalyst **II** (5 mol %) in the presence of $BF_3{\cdot}OEt_2$ (1 mol %). To our delight, the expected product **4a** was isolated in 99% yield, after continuous heating of the reaction mixture at 45 °C in a sealed tube for 4 days (Table 1, entry 4). The reaction time was dramatically reduced (20 min) when microwave irradiation was employed (Table 1, entry 5). Once reaction conditions had been optimized, we extended this tandem process to other alkyl vinyl ketones and protected amines. The results are summarized in Table 2. It is noteworthy that the tandem process is independent of the ketone substitution affording good to excellent chemical yields in the formation of both five- and six-membered rings.

The next step of our study was the extension of the tandem protocol to enantiomerically enriched substituted amines **7**. With this purpose, we prepared a set of α-branched Cbz-protected amines following known protocols (see Supporting Information), which were subjected to the tandem process, applying the optimized reaction conditions using methyl vinyl ketone **1a** as the enone component. The obtained results are summarized in Table 3.

Once again the overall process was very efficient, providing excellent chemical yields in all cases albeit with moderate selectivity in the formation of the newly created stereocenter.[17] After continuous heating for 4 days (thermal conditions), diastereoisomers **8a**−**d** (with trans relative disposition) are formed to a major extent. Interestingly, the stereochemistry found in the final products, when the reaction was performed under microwave irradiation, was reverse, with compounds **9a**−**d** (with cis relative disposition) as the major diastereoisomers.[18]

In summary, we have developed the first cross metathesis intramolecular aza-Michael tandem reaction, catalyzed by a Hoveyda−Grubbs second generation catalyst (**II**)/$BF_3{\cdot}OEt_2$ system, that allows rapid access to protected 2,5-substituted pyrrolidine and 2-substituted piperidine heterocyles with excellent overall yields. Microwave irradiation effectively accelerates the tandem process, producing an inversion of the selectivity when α-substituted amines were used as starting materials. These *β*-amino carbonyl units are very interesting building blocks for the synthesis of several alkaloids. In addition, the tandem protocol constitutes one of the few intramolecular aza-Michael reactions of Cbz-protected amines reported in the literature, thus becoming a straightforward methodology to access such compounds. New applications of this methodology are currently under study.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews see: (a) De Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (d) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 365. (e) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302.
(2) (a) Grubbs, R. H. In *Handbook of Metathesis*; Wiley-VCH Verlag Gmbh and Co. KGaA: Weinheim, Germany, 2003; Vol. 1−3. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.
(3) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.
(4) (a) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; Del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706. (b) Schmidt, B. *Chem. Commun*. **2004**, 742. (c) Schmidt, B. *J. Org. Chem*. **2004**, *69*, 7672. (d) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. (e) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390.
(5) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439.
(6) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc*. **2005**, *127*, 16329.
(7) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900.
(8) Liu, Z.; Rainier, J. D. *Org. Lett*. **2006**, *8*, 459.
(9) Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett*. **2006**, *8*, 2603.
(10) Clark, D. A.; Kulkarni, A. A., Kalbarczyk, K.; Schertzer, B.; Diver, S. T. *J. Am. Chem. Soc*. **2006**, *128*, 15632.
(11) Kim, G. B.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52.
(12) Randa, S.; Buschmann, N.; Connon, S. J.; Blechert, S. *Synlett* **2001**, *10*, 1547.
(13) (a) de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkov, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, 3105. (b) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. (d) Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A. *Synlett* **1992**, 962. (e) Hirama, M. J. *Synth. Org. Chem. Jpn*. **1987**, *45*, 346.
(14) (a) McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett*. **2000**, *41*, 1849. (b) Takeuchi, Y.; Tokuda, S.; Takagi, T.; Koike, M.; Abe, H.; Harayama, T.; Shibata, Y.; Kim, H.-S.; Wataya, Y. *Heterocycles* **1999**, *51*, 1869. For chiral Lewis acids, see: (c) Nakama, K.; Seki, S.; Kanemasa, S. *Tetrahedron Lett*. **2002**, *43*, 829. (d) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **2001**, 1240. (e) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1999**, *121*, 8959. (f) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615. (g) Falborg, L.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823.
(15) Vedrenne, E.; Dupont, H.; Oualef, S.; Elkäim, L.; Grimaud, L. *Synlett* **2005**, 270.
(16) Kobayashi, S.; Kakumoto, K.; Sugiera, M. *Org. Lett*. **2002**, *4*, 1319.
(17) The relative stereochemistry of the newly created stereocenter was determined by NOESY experiments over compounds **8a** and **9a** (see Supporting Information).
(18) A solvent study over substrate **7a** was performed (with the process under microwave irradiation). The reaction was carried out in DCM, toluene, THF, and acetonitrile. The best results in terms of selectivity and yield were obtained in DCM.

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