

Dynamic Kinetic Asymmetric Transformation (DYKAT) by Combined Amine- and Transition-Metal-Catalyzed Enantioselective Cycloisomerization

Gui-Ling Zhao,^[a] Farman Ullah,^[a] Luca Deiana,^[a] Shuangzheng Lin,^[a] Qiong Zhang,^[c] Junliang Sun,^[b] Ismail Ibrahim,^[a] Pawel Dziedzic,^[a] and Armando Córdoba*^[a]

Abstract: The first examples of one-pot highly chemo- and enantioselective dynamic kinetic asymmetric transformations (DYKATs) involving α,β -unsaturated aldehydes and propargylated carbon acids are presented. These DYKATs, which proceed by a combination of catalytic iminium activation, enamine activation, and Pd⁰-catalyzed enyne cycloisomerization, give access to functionalized cyclopentenones with up to 99% *ee* and can be used for the generation of all-carbon quaternary stereocenters.

Keywords: asymmetric synthesis • cyclopentenones • dynamic kinetic transformation • organocatalysis • transition-metal catalysis

Introduction

Cascade and domino reactions that involve the formation of multiple carbon-carbon or carbon-heteroatom bonds in one-pot fashion can be synthetically useful and allow the synthesis of small molecules with complex molecular scaffolds.^[1] The advantages of domino reactions include important factors such as atom economy,^[2] reduction of synthetic steps, and minimization of solvents and waste.^[3] Whereas several elegant cascade sequences catalyzed by single chemical entities have been described,^[1] far fewer reports on the use of combinations of more than one compatible catalyst for reaction sequences exist.^[4]

In this context, the development of asymmetric dual catalytic systems for cascade reactions is even more challenging. Dual applications of metal-based and metal-free catalysis in dynamic kinetic transformation (DYKAT) processes are very few.^[5] A DYKAT process overcomes the disadvantage of the maximum 50% theoretical yield obtainable from a kinetic resolution. One example is the combination of metal- and enzyme-based catalysis used by Bäckvall and co-workers, which proceeds through de-epimerization of diastereoisomers (type III).^[5a–b] To the best of our knowledge, no example of dual metal-based catalysis and organocatalysis involving epimerization of diastereoisomers through (reversible) destruction of both centers to yield two achiral intermediates (type IV) has yet been reported.^[5a,c,d] The development of organocatalytic asymmetric one-pot cascade and domino reactions based on (single or multiple) amine-based organocatalysts is a rapidly growing research area.^[6] The key activation modes are: i) enamine activation^[7] of carbonyl compounds, and ii) iminium activation^[8] of α,β -unsaturated carbonyl compounds. The combination of these activation modes has produced impressive results, with the formation of complex molecules from simple starting materials.

In parallel, the field of transition-metal-catalyzed cascade sequences is continuing to grow and develop. One area in particular is that of cascade reactions involving alkyne functionality, in which transition metal ions are employed to provide the necessary activation to trigger the process.^[9]

In 2006, we successfully developed a merged catalytic dual system based on enamine activation and Pd⁰ catalysis for the direct α -allylation of ketones and aldehydes.^[10] In the same research area,^[11,12] Kirsch recently showed that en-

[a] Dr. G.-L. Zhao, Dr. F. Ullah, L. Deiana, Dr. S. Lin, Dr. I. Ibrahim, P. Dziedzic, Prof. Dr. A. Córdoba
Department of Organic Chemistry, The Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
Fax: (+46) 8-154908
E-mail: acordova@organ.su.se

[b] Prof. Dr. J. Sun
Department of Structural Chemistry, The Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
and Berzelii Center EXSELENT on Porous Materials
The Arrhenius Laboratory, Stockholm University
106 91 Stockholm (Sweden)

[c] Q. Zhang
Department of Theoretical Chemistry School of Biotechnology
Royal Institute of Technology, Roslagstullsbacken 15
10691 Stockholm (Sweden)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200902818>.

amine activation of ketones could be combined with gold catalysis to give racemic cyclopentenones.^[11d] At almost the same time, Dixon reported elegant cascade reactions between α,β -unsaturated ketones and propargylated carbon acids based on a combination of achiral amine and copper(I) catalysis.^[11e] As a result of our research experience in dual-catalysis and DYKATs, we became interested in the challenging strategy of developing a process, based on a combination of amine catalysis and transition metal catalysis (Scheme 1), for highly enantioselective DYKATs between α,β -unsaturated aldehydes and activated carbonyl compounds such as propargylated carbon acids for the construction of complex stereodefined small molecules.

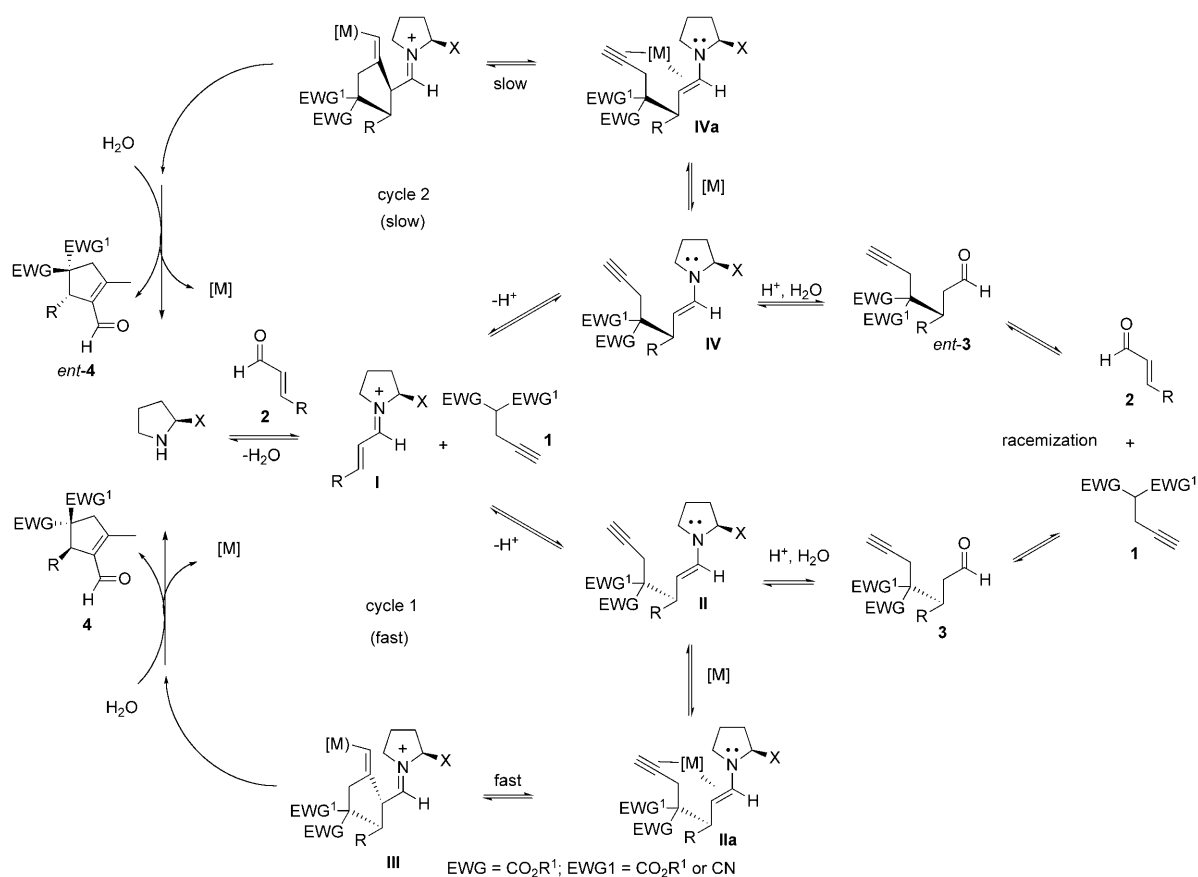
The reaction design would enable multiple C–C bond formation by first allowing in situ generation of the catalytic iminium intermediates **I**, derived from enals **2**. These would undergo nucleophilic conjugate attack by the alkyne-tethered nucleophiles **1**, followed by generation of chiral enamine intermediates **II** (Scheme 1, cycle 1) or **IV** (cycle 2). Notably, this conjugate step is reversible and the corresponding Michael adducts **3** and *ent*-**3** are formed in equal amounts (0% *ee*). Indeed, the chiral amine **5** catalyzed the metal-free Michael reactions between nucleophiles **1** and enals **2** with no enantioselectivity to form products **3** with 0% *ee* in CH_3CN at room temperature.^[13] Next, catalytic activation of the alkynyl functional groups by a metal complex would

generate electrophilic species and allow for subsequent stereoselective intramolecular cycloisomerization with the chiral enamine intermediates **IIa** or **IVa**. If the rate of the non-reversible oxidative cycloaddition were faster in the case of **IIa** than in that of **IVa**, cycle 1 would be faster than cycle 2 and the optically active cyclopentene derivatives **4** would be formed after protonolysis, subsequent hydrolysis of the iminium intermediates **III**, and double bond isomerization. This would also regenerate the metal and amine catalysts, so that the DYKAT could proceed.

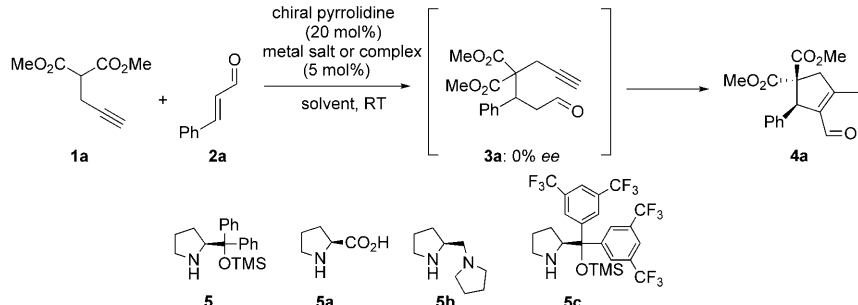
Results and Discussion

Here we describe the first highly enantioselective dynamic kinetic asymmetric transformations (DYKATs) based on a one-pot combination of catalytic iminium activation, enamine activation, and Pd^0 -catalyzed enyne cycloisomerization.

We initially treated dimethyl propargylmalonate (**1a**, 0.375 mmol) and cinnamaldehyde (**2a**, 0.25 mmol) in the presence of a catalytic amount of $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol %) and of chiral pyrrolidines (20 mol %) in MeOH or CH_3CN (0.6 mL) at room temperature (Table 1). To our delight, we found that protected diarylprolinol derivatives such as **5**^[14] catalyzed the reaction with excellent chemoselectivity and high enantioselectivity to form the corresponding cyclopenten-



Scheme 1. Combined transition-metal- and amine-catalyzed DYKAT.

Table 1. Combined palladium- and chiral amine-catalyzed asymmetric DYKAT.^[a]


Entry	Metal salt	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	[Pd(PPh ₃) ₄]	MeOH	46	22	94
2	AgOTf+PPh ₃	MeOH	120	<5	n.d.
3	AgOTf+PPh ₃	MeOH	192	11	82
4	[Au(PPh ₃)Cl]	MeOH	16	22 ^[d]	0 ^[g]
5	[Cu(OTf) ₂]+PPh ₃	MeOH	192	—	—
6	[Au(PPh ₃)Cl]+[Pd(PPh ₃) ₄]	MeOH	48	—	—
7	[(PPh ₃)AuSbF ₆]	CHCl ₃	48 ^[h]	—	—
8	[Pd(PPh ₃) ₄]	EtOH	136	26	96
9	[Pd(PPh ₃) ₄]	CHCl ₃	88	45	94
10	[Pd(PPh ₃) ₄]	CH ₂ Cl ₂	64	29	97
11	[Pd(PPh ₃) ₄]	ClCH ₂ CH ₂ Cl	88	42	98
12	[Pd(PPh ₃) ₄]	CH ₃ CN	40	48 (80) ^[e]	98
13	[Pd(PPh ₃) ₄]	CH ₃ CN	24	53 ^[f]	91 ^[f]
14	none	CH ₃ CN	24	23 ^[d]	0 ^[g]
15	[Pd(PPh ₃) ₄]	CH ₃ CN ^[i]	66 ^[j]	0 ^[i]	0 ^[i]
16	[Pd(PPh ₃) ₄]	CH ₃ CN	72 ^[j]	26 ^[j]	<5 ^[j]
17	[Pd(PPh ₃) ₄]	CH ₃ CN	88 ^[k]	22 ^[k]	92 ^[k]

[a] Experimental conditions: a mixture of **1a** (0.75 mmol) and Pd(PPh₃)₄ (5 mol %) in solvent (1.2 mL) was stirred for 5 min. Next, aldehyde **2a** (0.5 mmol) and amine **5** (20 mol %) were added and the reaction mixture was stirred at room temperature for the time shown in the table. [b] Isolated yield of the corresponding aldehyde **4a** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] The Michael product **3a** was formed. [e] Yield based on recovered starting material. [f] Reaction volume was 0.3 mL. [g] The *ee* of Michael product **3a**. [h] Reaction run at 70 °C. [i] Reaction run with chiral amine **5a**. [j] Reaction run with chiral amine **5b**. [k] Reaction run with chiral amine **5c**.

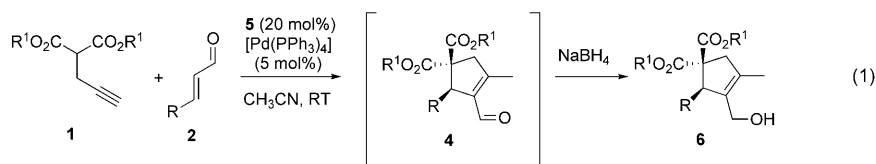
tene **4a** as the only product together with remaining aldehyde **2a** (Table 1).

Other metal salts were also investigated and we found that Ag^I was able to co-catalyze the reaction together with **5** with high chemo- and enantioselectivity (entries 2 and 3). However, the reaction was slower than those with Pd⁰ as the co-catalyst and the corresponding product was isolated in low yield and with 82 % *ee* (entry 3). With Cu and Au salts as co-catalysts the reactions did not afford **4a** as a product under our reaction conditions (entries 4–7). In the case in which Au(PPh₃)Cl was employed as the co-catalyst, the corresponding Michael product **3a** was formed with 0 % *ee* (entry 4). No products were formed in the cases of entries 5 and 6, however, which is possibly due to inhibition of the catalytic iminium species by the metal complex. Indeed, the Michael product **3a** was formed with 0 % *ee* even if the metal complex was not added (entry 14). On the basis of on these findings, the co-

catalytic system of Pd⁰^[15] and pyrrolidine **5** was further optimized in various solvents (entries 8–12). The yields were improved when the cascade reaction was run in CHCl₃, ClCH₂CH₂Cl, or CH₃CN (entries 9, 11, and 12); compound **4a** was isolated in 48 % yield (80 % based on recovered **2a**) with 98 % *ee* in CH₃CN, for example (entry 12). Running the reaction at higher concentration increased the rate and yield but slightly decreased the enantioselectivity of the reaction, with **4a** being obtained with 91 % *ee* (entry 13). Encouraged by these initial results, we decided to investigate combined transition-metal- and amine-catalyzed DYKATs for a set of simple enals **2** (Table 2).

The reactions proceeded smoothly, giving the corresponding cyclopentenones **4a–k** in moderate to high yields with excellent chemoselectivities and high enantioselectivities (93–99 % *ee*). In some cases, the starting material **1** was difficult to separate from the product **4**, and so these cyclopentenones were chemoselectively

reduced with NaBH₄ in situ to afford the corresponding alcohols **6** [Eq. (1)]. The opposite enantiomers were readily assembled by employing *ent*-**5** as the catalyst.



The development of methods for the formation of all-carbon quaternary stereocenters is an important and difficult task in organic synthesis.^[16] Notably, the combined metal-catalyzed and organocatalyzed DYKAT was employed for the formation of cyclopentenones **4** containing all-carbon quaternary stereocenters (Table 3). The reactions between **1b** and enals **2** thus gave the corresponding cyclopentenones **4l–o** with good to excellent diastereoselectivities and high enantioselectivities (entries 1–4). The relative stereochemistry of **4m** was established by NOE experiments, which con-

Table 2. Combined palladium- and amine-catalyzed DYKAT of enals **2**.^[a]

Entry	R	R ¹	t [h]	Prod.	Yield [%] ^[b]	ee [%] ^[c]
1		Me	40	4a	48 ^[d]	98
2		Me	44	4b	83	98
3		Me	24	4c	62 ^[e]	99
4		Me	46	4d	70	96
5		Me	24	4e	66 ^[e]	97
6		Me	63	4f	54 ^[d,f]	99
7		Et	48	4g	77	98
8		Me	64	4h	70 ^[d]	98
9		Me	16	4i	86 ^[e]	97
10		Me	72	4j	39 ^[d,e]	95
11		Me	46	4k	63	93

[a] Experimental conditions: a mixture of **1** (0.75 mmol) and [Pd(PPh₃)₄] (5 mol %) in CH₃CN (1.2 mL) was stirred for 5 min. Next, aldehyde **2** (0.5 mmol) and amine **5** (20 mol %) were added and the reaction mixture was stirred at room temperature for the time shown in the table. [b] Isolated yield of the corresponding product **4** after silica gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] The isolated yield of corresponding alcohol **6** after in situ reduction of aldehyde **4** with excess NaBH₄. [e] Reaction volume was 0.3 mL. [f] Reaction volume was 0.6 mL.

firmed the relative configuration between the neighboring substituents.

The DYKAT reactions involving non-terminal alkyne nucleophiles are not limited to terminal alkynes, as shown in the synthesis of the pentenol **6o** [Eq. (2)] with 92 % *ee*.

The aldehydes **4** are also readily oxidized to the corresponding more stable acids **7** [Eq. (3)]. It is noteworthy that the highly chemoselective hydrolysis of the acid **7e** with two methyl ester groups gave the corresponding diacid **8e**

with an all-carbon quaternary stereocenter as a single diastereoisomer. We also performed X-ray analysis of the oxime **9e**^[17] and assigned the absolute configuration of acid **7i** as *R* with the aid of TD-DFT calculations of the electronic circular dichroism (ECD) spectra.^[18] The absolute configuration was also established by X-ray analysis of acid **8e**.^[17] From this, we propose the following mechanism for the reaction pathway. Two potential catalytic cycles can thus operate in the reactions between nucleophiles **1** and enals **2** (Scheme 1). In the faster cycle, the major enantiomer product **4** is formed (cycle 1) and in the slower cycle the minor enantiomer *ent-4* is formed (cycle 2). The initial Michael step, which proceeds through the iminium intermediate **I**, is dynamic and reversible, leading to formation of the Michael product **3** and its mirror image *ent-3* in equal amounts (0 % *ee*). In the case of the DYKAT with nucleophile **1b**, the corresponding Michael adduct **3** was first formed in a 1:1 mixture with 0 % *ee*. All four possible enantiomers are therefore reversibly formed and destroyed, to afford the corresponding starting **1b** and enals **2** once more by the retro-Michael process

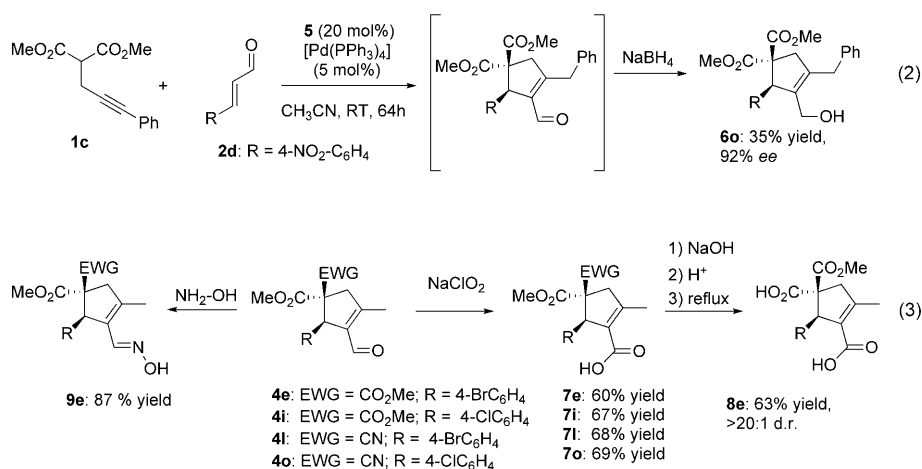
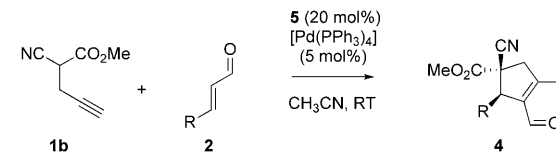


Table 3. Combined palladium- and amine-catalyzed DYKAT of enals **2**.^[a]


Entry	R	<i>t</i> [h]	Prod.	Yield [%] ^[b]	d.r. ^[c]	<i>ee</i> [%] ^[d]
1		16	4l	59	7:1	95
2		15	4m	60	12:1	86
3	Me	16	4n	56	3:1	92
4		16	4o	55	7:1	89

[a] Experimental conditions: a mixture of **1b** (0.75 mmol) and Pd(PPh₃)₄ (5 mol %) in CH₃CN (1.2 mL) was stirred for 5 min. Next, aldehyde **2** (0.5 mmol) and amine **5** (20 mol %) were added and the reaction mixture was stirred at room temperature for the time shown in the table. [b] Isolated yield of the corresponding product **4** after silica gel column chromatography. [c] Determined by ¹H NMR of the crude reaction mixture. [d] Determined by chiral-phase HPLC or GC analysis.

(DYKAT, type IV).^[5a] Next, because of the efficient shielding of the *Re*-face (*R*=Ar) of the chiral enamine intermediate **IIa** by the bulky aryl groups of **5**, a stereoselective *Si*-facial intramolecular cycloisomerization between the enamine and the metal-activated triple bond occurs instead of cycloaddition of the enamine intermediate **IV** originating from the slowly reacting enantiomer *ent*-**3**. This irreversible enantioselective step, involving both the metal and the amine catalysts, thus dictates the continuation of cycle 1 at a faster rate over entrance to cycle 2. For the Pd⁰-catalyzed cyclization of enamine **IIa** we propose the following two initiation mechanisms: either 1) oxidative addition of the solvent (HX) to palladium(0) (path A, Scheme 2), or 2) a cycloaddition reaction (path B, Scheme 2).^[19,20] Both paths in Scheme 2 are also similar to the two paths proposed for the palladium(0)-catalyzed cycloisomerizations of enynes.^[20] In accordance with this, the addition of solvent HY to Pd⁰ would give a Pd^{II} hydride species. This palladium (II) species can add to the alkyne to form a vinylpalladium intermediate (**A**). An insertion of the double bond into the palladium-carbon bond would give intermediate **B**, which would subsequently undergo a β-elimination to give the iminium intermediate **C** and—after hydrolysis and isomerization—product **4** (Scheme 2, path A). In this step, the Pd^{II} hydride species is regenerated and can again be coordinated to the enamine **IIa**, closing the catalytic cycle.

The cyclization of enamine **IIa** can also be explained by an oxidative cycloaddition of the enyne to palladium(0), forming the palladium(II) intermediate **D** (path B, Scheme 2). β-Elimination and protonation of Pd would give the iminium intermediate **E** and subsequent reductive hydride elimination would afford the iminium intermediate **C**. In this step, the Pd⁰ is regenerated and can perform the oxidative cycloaddition with the enamine **IIa** again and close the catalytic cycle. Hydrolysis and isomerization of the imi-

nium intermediate **C** gives the aldehyde product **4** and regenerates the amine catalysts **5**.

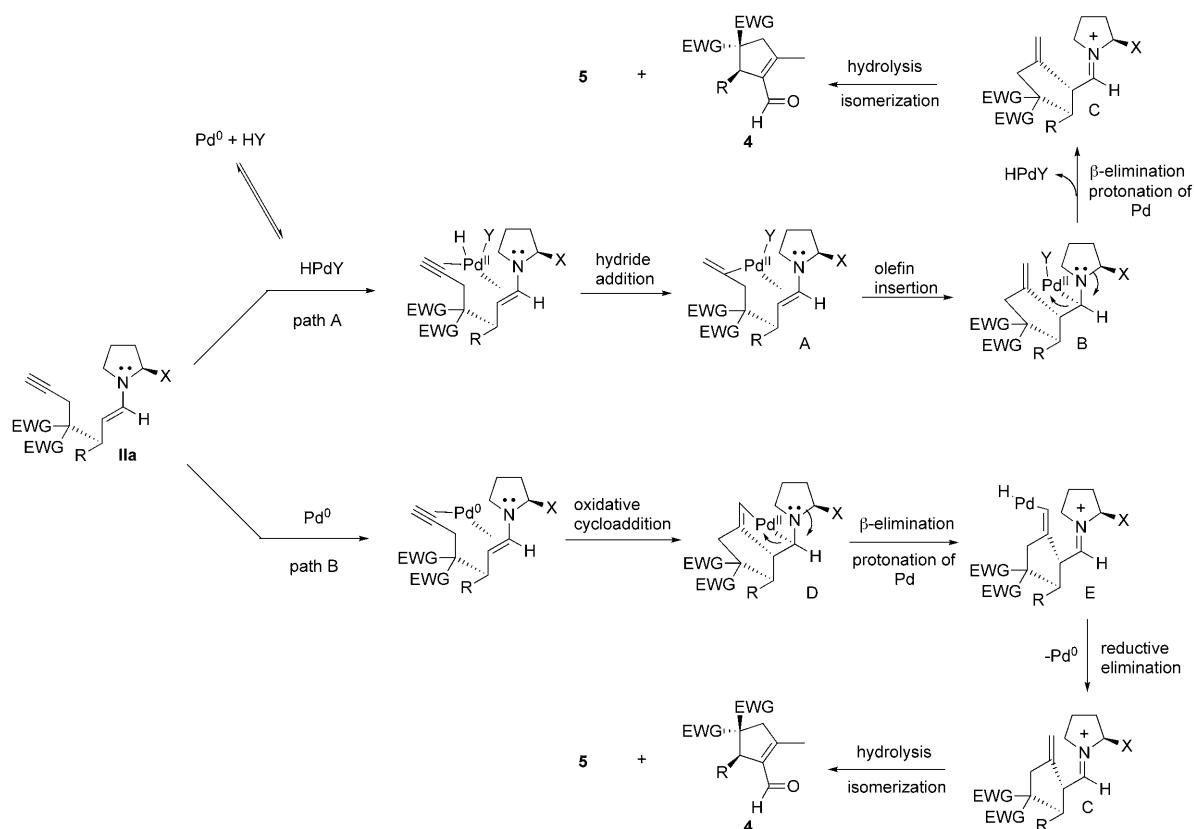
Performing the DYKAT in CD₃CN did not give the corresponding deuterated product **4**, which indicates that the oxidative cycloaddition to Pd⁰ (path B, Scheme 2) is predominant under our reaction conditions.

The Michael reactions between compounds **1** and **2**, catalyzed by the amines **5**, give the racemic products **3** (0% *ee*) under the conditions employed in the DYKAT. Furthermore, the co-catalyzed [by amine **5** and Pd⁰] reaction between **1a** and **2a** gave the corresponding Michael adduct **3a** and the cyclopentene **4a** in a

53:47 ratio with 0% and 94% *ees*, respectively, after 28 h. In addition, the intramolecular reaction of the isolated racemic product **3a** in the presence of a combination of Pd⁰ (5 mol %) and **5** (20 mol %) in CH₃CN gave the corresponding cyclopentene **4a** with 35% *ee*. We also performed the exact same reaction as described (*vide infra*), but changed the chiral amine **5** to a tertiary amine (such as *N,N*-diisopropylethylamine, DIPEA). The racemic product **3a** was thus treated in the presence of Pd⁰ (5 mol %) and DIPEA (20 mol %) in CH₃CN. No formation of **4a** was observed; instead the retro-Michael reaction occurred, and after 48 h cinnamaldehyde (**2a**) and **1a** had been formed in significant amounts. All of these experiments support the DYKAT mechanism (Scheme 1). We also showed that the one-pot reaction procedure is essential for achievement of excellent enantioselectivity. Running the same reaction in a sequential fashion, firstly by treating **1a** with **2a** in the presence of **5** (20 mol %) in MeOH, resulted after 22 h in the Michael adduct **3a** being formed, as determined by crude ¹H NMR analysis. Pd⁰ (5 mol %) was then added to the reaction mixture. The reaction was then quenched after an additional 20 h and the cyclopentene **4a** was isolated in 39% yield with 74% *ee*. The one-pot combination of iminium-, enamine- and Pd⁰-catalyzed enyne cycloisomerization is thus crucial for achieving a highly enantioselective DYKAT. The concentrations of substrates and products are completely different in the sequential procedure and this will affect the selectivity of the DYKAT process.

Conclusion

In summary, we have developed a simple and highly enantioselective DYKAT procedure (of type IV) utilizing propargylated carbon acids and enals with the aid of a one-pot



Scheme 2.

combination of asymmetric amine catalysis and transition metal catalysis. Catalytic iminium activation, enamine activation, and transition-metal-catalyzed enyne cycloisomerization can thus be efficiently merged for the development of DYKATs and the formation of all-carbon quaternary stereocenters with high stereoselectivity. We are currently focusing on the following topics: a) expansion of the concept of one-pot combinations of transition metal and amine catalysis to other metals and reactants, and b) development of catalytic asymmetric reactions through the employment of simple and inexpensive optically active amine catalysts and/or chiral metal ligands. Preliminary results will be communicated in due course.

Acknowledgements

Professor Jan-E. Bäckvall is acknowledged for valuable discussions. We gratefully acknowledge the Swedish National Research Council and the Wenner-Gren-Foundation for financial support. The Berzelii Center EX-SELENT is financially supported by VR and the Swedish Governmental Agency for Innovation Systems (VINNOVA). We also thank Professor Astrid Gräslund and Dr. Jesper Lind for time on the CD spectropolarimeter.

- [1] For reviews on this concept, see: a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim **2006**, p. 672; b) L. F. Tietze, *Chem. Rev.* **1996**, 96, 115; c) K. C.

Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, 118, 7292; *Angew. Chem. Int. Ed.* **2006**, 45, 7134; d) H. Guo, J. Ma, *Angew. Chem.* **2006**, 118, 362; *Angew. Chem. Int. Ed.* **2006**, 45, 354; e) H. Pellissier, *Tetrahedron* **2006**, 62, 2143; f) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, 117, 1628; *Angew. Chem. Int. Ed.* **2005**, 44, 1602.

- [2] a) B. M. Trost, *Science* **1991**, 254, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, 107, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 259.
[3] a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **2000**, p. 135; b) For an excellent paper on combining one-pot, step reduction and atom economy in organic chemistry, see: P. A. Clarke, S. Santos, W. H. C. Martin, *Green Chem.* **2007**, 9, 438.
[4] For reviews on multi-catalyst cascades, see: a) S. F. Mayer, W. Kroutil, K. Faber, *Chem. Soc. Rev.* **2006**, 35, 332; b) L. Veum, U. Hanefeld, *Chem. Commun.* **2006**, 825; c) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, 33, 302. For selected examples, see: d) M. Sawamura, M. Sudoh, Y. Itoh, *J. Am. Chem. Soc.* **1996**, 118, 3309; e) B. G. Jellerichs, J.-R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2003**, 125, 7758; f) B. M. Trost, E. J. McEachern, F. D. Toste, *J. Am. Chem. Soc.* **1998**, 120, 12702; g) M. Edin, J.-E. Bäckvall, A. Córdova, *Tetrahedron Lett.* **2004**, 45, 7697.
[5] For an excellent review on the topic of DYKATs and classification of them, see: a) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, 14, 8060. For DYKAT type III by combination of metal and enzyme catalysis, see: b) M. Edin, J. Steinreiber, J.-E. Bäckvall, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5761. For the only two examples of DYKAT type IV, see: c) E. Reyes, A. Córdova, *Tetrahedron Lett.* **2005**, 46, 6605; d) J. Steinreiber, M. Schurmann, M. Wolberg, F. van Assema, C. Reisinger, K. Fesko, D. Mink, H. Griengl, *Angew. Chem.* **2007**, 119, 1648; *Angew. Chem. Int. Ed.* **2007**, 46, 1624.
[6] For reviews on organocatalytic domino reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, 119, 1590; *Angew.*

- Chem. Int. Ed.* **2007**, *46*, 1570; b) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037. For selected examples of organocatalytic asymmetric domino and cascade reactions, see: c) N. Halland, P. S. Abur-ell, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1292; *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; d) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; e) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *J. Am. Chem. Soc.* **2005**, *127*, 15036; f) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; g) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; h) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem.* **2003**, *115*, 4365; *Angew. Chem. Int. Ed.* **2003**, *42*, 4233; i) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; j) H. Sundén, I. Ibrahim, L. Eriksson, A. Córdova, *Angew. Chem.* **2005**, *117*, 4955; *Angew. Chem. Int. Ed.* **2005**, *44*, 4877; k) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; l) H. Sundén, I. Ibrahim, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 99; m) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928; n) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354; o) R. Rios, H. Sundén, I. Ibrahim, G.-L. Zhao, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2006**, *47*, 8547; p) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; q) J. Wang, H. Li, H. Xie, L. Zu, X. Shen, W. Wang, *Angew. Chem.* **2007**, *119*, 9208; *Angew. Chem. Int. Ed.* **2007**, *46*, 9050.
- [7] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471.
- [8] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416.
- [9] For a review, see: a) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431. For selected examples, see: b) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627; c) S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, D. D. Toste, *Angew. Chem.* **2006**, *118*, 6137; *Angew. Chem. Int. Ed.* **2006**, *45*, 5991; d) T. Yang, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2007**, *129*, 12070; e) P. Magnus, B. Mugrage, M. DeLuca, G. A. Cain, *J. Am. Chem. Soc.* **1989**, *111*, 786; f) T. J. Harrison, B. O. Patrick, G. R. Dake, *Org. Lett.* **2007**, *9*, 367.
- [10] I. Ibrahim, A. Córdova, *Angew. Chem.* **2006**, *118*, 1986; *Angew. Chem. Int. Ed.* **2006**, *45*, 1952.
- [11] a) F. Bihelovic, R. Matovic, B. Vulovic, R. N. Saicic, *Org. Lett.* **2007**, *9*, 5063; b) S. Mukharjee, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 1136; c) Q. Ding, J. Wu, *Org. Lett.* **2007**, *9*, 367; d) J. Binder, B. Crone, T. T. Haug, H. Menz, S. F. Kirsch, *Org. Lett.* **2008**, *10*, 1025; e) T. Yang, A. Ferrali, L. Campbell, D. J. Dixon, *Chem. Commun.* **2008**, 2923. See also: f) D. J. Weix, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 7720; g) D. Liu, F. Xie, W. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4959; h) I. Usui, S. Schmidt, B. Breit, *Org. Lett.* **2009**, *11*, 1453. For reviews on this topic, see: i) A. Duschek, S. F. Kirsch, *Angew. Chem.* **2008**, *120*, 5787; *Angew. Chem. Int. Ed.* **2008**, *47*, 5703; j) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745.
- [12] For other types of selected examples of combination of metal and organocatalysis, see: a) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 3329; b) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *J. Org. Chem.* **2002**, *67*, 7418; c) I. Ibrahim, J. S. M. Samec, J. E. Bäckvall, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3965; d) D. A. Nicewicz, D. W. A. MacMillan, *Science* **2008**, *322*, 77; e) E. J. Kang, M. Mba, D. F. Toste, *Science* **2007**, *317*, 496; f) M. Rueping, A. P. Antonchick, C. Brikmun, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903; g) O. Abillard, B. Breit, *Adv. Synth. Catal.* **2007**, *349*, 1891, S. Chercheja, P. Eilbracht, *Adv. Synth. Catal.* **2007**, *349*, 1897; h) I. Usui, S. Schmidt, B. Breit, *Org. Lett.* **2009**, *11*, 1453; i) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140.
- [13] The lack of stereoselectivity in the chiral amine **5**-catalyzed Michael transformation under our reaction conditions is explained by that the bulky alkyne group of the nucleophiles **1** favors fast racemization of the products **3** possibly by Michel/retro-Michael reactions to give **3** with 0% ee.
- [14] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. For a review, see: c) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.
- [15] The initial palladium complexes were: in situ generated [Pd(PPh₃)₄] or commercially available [Pd(PPh₃)₄].
- [16] For selected reviews on quaternary stereocenters, see: a) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591; b) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369; c) J. Christoffers, A. Baron, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim **2006**; d) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969.
- [17] CCDC-725913 and CCDC-755830 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [18] For the TD-DFT calculated and experimental electronic circular dichroism (ECD) spectra see the Supporting Information: For an excellent review on examples of this method, see: N. Berova, L. Di Bari, G. Pescitelli, *Chem. Soc. Rev.* **2007**, *36*, 914.
- [19] K. Närhi, J. Franzén, J.-E. Bäckvall, *Chem. Eur. J.* **2005**, *11*, 6937, and references therein.
- [20] a) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34; b) B. M. Trost, D. C. Lee, F. Rise, *Tetrahedron Lett.* **1989**, *30*, 651; c) B. M. Trost, D. L. Romero, F. Rise, *J. Am. Chem. Soc.* **1994**, *116*, 4268; d) B. M. Trost, L. Dong, G. M. Schroeder, *J. Am. Chem. Soc.* **2005**, *127*, 10259; e) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813.

Received: October 13, 2009
Published online: December 28, 2009