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Relay catalysis: combined metal catalyzed oxidation and asymmetric iminium catalysis for the synthesis of bi- and tricyclic chromenes†

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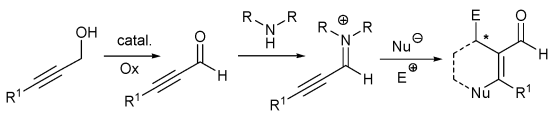
A catalytic asymmetric oxidative iminium–allenamine cascade allows the use of propargyl alcohols as stable substrates and yields valuable chiral bicyclic 4*H*-chromenes. A subsequent Michael addition–condensation domino reaction provides complex tricyclic 4*H*-chromenes in a highly enantioselective fashion.



Scheme 1 Combined metal and organocatalytic reactions.

One-pot multi-component domino reactions are of great interest in organic synthesis as they allow the creation of complex structures by sequential transformations from simple starting materials. These atom-economical cascades achieve desirable time and cost saving by avoiding protecting group manipulations and tedious purification of the intermediates. Among these processes, asymmetric organocatalytic cascades proceeding through a combination of iminium and enamine activations have been widely investigated over the past few years.[1] They mainly rely on the activation of unsaturated aldehydes by chiral secondary amines catalysts and afford complex molecules by addition of various electrophiles and nucleophiles.

However, it is well known that aldehydes have to be purified prior to use in organocatalysis in order to obtain good levels of reactivity and enantioselectivity. Moreover, aldehydes are sensitive to storage, and non-commercial aldehydes are commonly obtained by oxidation of alcohols. Thus, the use of allylic or propargylic alcohols would be highly convenient and synthetically useful. Indeed, generating the aldehyde *in situ via* oxidation would without doubt extend the scope of organocatalyzed reactions.

In general one-pot tandem oxidative processes involving an alcohol have been established; however they are mainly limited to oxidation/Wittig olefinations or to the formation of diverse heterocycles.[2] Asymmetric Lewis base catalyzed reactions involving the *in situ* catalytic oxidation of alcohols have not been reported to date.

In combination with enamine catalysis, Alexakis and Mazet reported a iridium catalyzed isomerization of allylic aldehydes followed by an organocatalyzed α-functionalization.[3] A stoichiometric oxidation of an enamine intermediate derived from an aldehyde and subsequent reaction with a nucleophile was reported independently by Hayashi *et al.*[4a] and Wang *et al.*[4b] during our investigations. In these reactions aldehydes which are often sensitive to air and moisture were applied and, additionally, rather expensive oxidants were used which needed to be separated by column chromatography.

We became interested in merging a catalytic oxidative process for the *in situ* formation of propargylic aldehydes with a secondary amine-catalyzed enantioselective cascade (Scheme 1). However, we felt that only the successful incorporation of the catalytic oxidation into a more complex reaction sequence would be an ideal demonstration that the combination of two distinct catalytic cycles, the metal catalyzed oxidation and domino Lewis base catalysis, is indeed viable. Thus, for demonstrating the feasibility of the combined catalysis concept we chose to develop a metal catalyzed oxidation of the propargylic alcohols followed by an iminium–allenamine activation[5,6] initially reported by Wang and Alemán.[6a,c] The reaction sequence allows the use of readily available and stable propargylic alcohols as precursors and prevents the necessary purification or distillation steps typically associated with the use of aldehydes in organocatalysis.

The initial challenge of this combined catalysis procedure was to find a mild and substrate-selective catalytic oxidative system that could be adaptable to chiral secondary amine catalytic cycles. During our investigations, we were pleased to discover that the catalytic oxidative system tetrapropylammonium perruthenate, TPAP,[7] associated with *N*-methylmorpholine-*N*-oxide (NMO) was compatible with secondary amine catalyst as well as substrates, intermediates and sensitive products. As shown in Scheme 2, initial oxidation of propargyl alcohol **2** yields the propargyl aldehyde while releasing one equivalent of *N*-methylmorpholine (NMM). The aldehyde is then transformed into the iminium ion **A** by condensation with the secondary amine catalyst.[8] Intermediate **A** can undergo an oxa-Michael addition with **1**. The resulting allenamine intermediate **B** reacts with the nitroalkene moiety by an intramolecular Michael addition leading to compound **3** after releasing the catalyst.[6]

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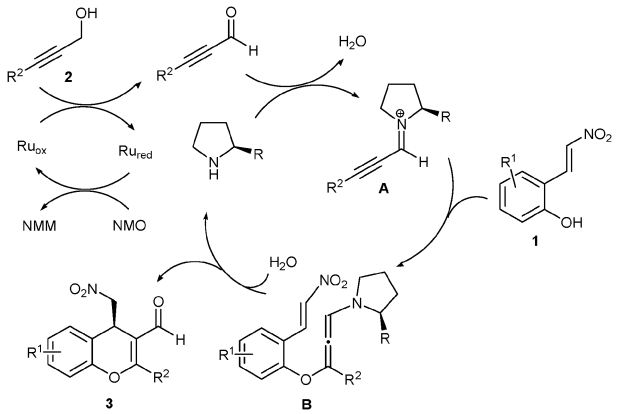
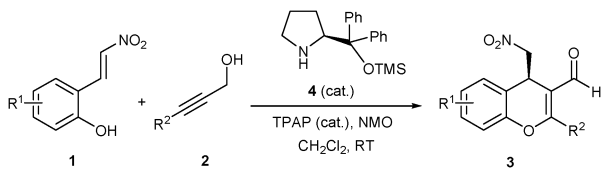


Scheme 2 Combined catalysis: metal- and organocatalysis.

Thus, it is most important to note that the TPAP/NMO system is compatible with both, the diarylprolinolsilyl ethers[8] as well as reaction intermediates. Moreover, the base released in the reaction mixture (NMM) was not detrimental to the domino reaction. After a thorough screening of solvents, temperature, stoichiometry of starting material and catalysts, optimal conditions for the oxidative iminium–enamine cascade reaction were found. The reaction between (*E*)-2-(2-nitrovinyl)-phenol **1a** and 3-phenylprop-2-yn-1-ol **2a** (1.5 equiv.) with 7 mol% of TPAP, NMO (1.6 equiv.) and catalyst **4** in CH_2Cl_2 yielded 4*H*-chromene derivative **3a** in good yield and excellent enantiomeric excess (95% ee) (Table 1, entry 1).

With the optimized conditions in hand, we investigated the scope of our newly developed triple cascade. For this purpose, several aryl-, alkenyl- and alkyl-substituted propargyl alcohols **2a–m** were reacted with (*E*)-2-(2-nitrovinyl)phenol **1a** to provide **3a–m** (Table 1, entries 1–13). Heteroaryl- and aryl propargyl alcohols bearing electron donating as well as withdrawing groups reacted smoothly to provide the products with good yields and excellent enantioselectivities (Table 1, entries 1–8). To our delight, the application of alkyl substituted propargyl alcohols also provided the chromenes with excellent yields and with the highest enantioselectivities (99% ee, entry 10). Limitations were found as propargyl alcohol bearing an ester function did not work under our reaction conditions. After extensive evaluation of propargyl alcohols, we devoted our attention to the variation of the nitrostyrene derivatives. Under the optimized conditions, different nitrostyrenes were reacted with **2a** to provide molecules **3n–r** (Table 1, entries 14–18) again with high yield and with excellent enantioselectivity.

Table 1 Scope of the catalytic enantioselective oxidative cascade



Entry[a]	1	R^1	2	R^2	3	Yield[b] (%)	ee[c] (%)
1	**1a**	H	**2a**	Ph	**3a**	81	95
2	**1a**	H	**2b**	4-(MeO_2C)–C_6H_4	**3b**	86	96
3	**1a**	H	**2c**	4-NO_2–C_6H_4	**3c**	77	95
4	**1a**	H	**2d**	4-Br–C_6H_4	**3d**	80	97
5	**1a**	H	**2e**	4-*t*-Bu–C_6H_4	**3e**	80	95
6	**1a**	H	**2f**	4-MeO–C_6H_4	**3f**	70	96
7	**1a**	H	**2g**	3-MeO–C_6H_4	**3g**	84	96
8	**1a**	H	**2h**	2-MeO–C_6H_4	**3h**	49	91
9	**1a**	H	**2i**	2-Thienyl	**3i**	92	96
10	**1a**	H	**2j**	1-Cyclohexenyl	**3j**	90	99
11	**1a**	H	**2k**	Cyclohexyl	**3k**	95	97
12	**1a**	H	**2l**	*t*-Bu	**3l**	96	98
13	**1a**	H	**2m**	$TBSOCH_2$	**3m**	53	92
14	**1b**	4-OMe	**2a**	Ph	**3n**	74	94
15	**1c**	5-OMe	**2a**	Ph	**3o**	74	97
16	**1d**	4-Br	**2a**	Ph	**3p**	84	96
17	**1e**	4-Me	**2a**	Ph	**3q**	74	97
18	**1f**	6-Me	**2a**	Ph	**3r**	71	77

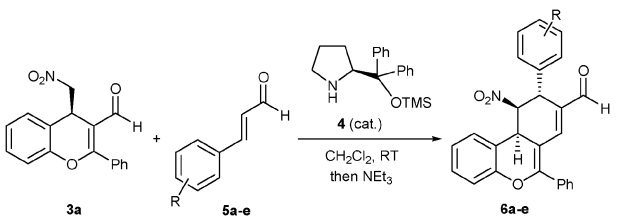
[a] Reaction conditions: 2-Hydroxynitrostyrene **1**, propargyl alcohol **2** (1.5 equiv.), TPAP (7 mol%), NMO (1.6 equiv.) and catalyst **4** (20 mol%) in CH_2Cl_2 at RT for 12 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC.

The enantiopure derivatives **3** prepared by our oxidative cascade are valuable compounds since they possess the 4*H*-chromene framework which is widespread in biologically active natural products and medicinal compounds.[9–11] To demonstrate the utility of **3**, we became interested in building more complex 4*H*-chromene derivatives enantioselectively by taking advantage of the present reactive functionalities (*i.e.* nitroalkane and aldehyde). The nitroalkane Michael addition to α,β-unsaturated aldehydes *via* secondary amine catalysis has been used with subsequent aldol reactions in several double, triple or quadruple cascades.[12–14] Thus compound **3a** was reacted with cinnamaldehyde in the presence of diarylprolinol TMS-ether catalyst **4** to afford 4*H*-chromene derivative **6a** as a mixture of two diastereoisomers.

After considerable reaction optimization the addition of triethylamine proved to be beneficial and only one isomer of **6a** could be obtained (77% yield, Table 2, entry 1). We assume that the base helps epimerizing the more acidic chiral center, α to the nitro group, to afford the more stable thermodynamic product. The organocatalytic cascade was performed with cinnamaldehydes **5b–e** to enlighten the generality of the reaction (Table 2).

The absolute configuration of the tricyclic 4*H*-chromene compounds was unambiguously determined by X-ray crystallographic

Table 2 Scope of the Michael–aldol condensation reaction



Entry[a]	Cinnamaldehyde	R	Product	Yield[b] (%)
1	**5a**	H	**6a**	77
2	**5b**	4-OMe	**6b**	84
3	**5c**	4-NO_2	**6c**	81
4	**5d**	4-Br	**6d**	78
5	**5e**	2-Br	**6e**	85

[a] Reaction conditions: Chromene derivative **3a**, cinnamaldehyde **5** (1.5 equiv.), and catalyst **4** (20 mol%) in CH_2Cl_2 at RT for 48 h followed by addition of NEt_3 (2.0 equiv.). [b] Yield after column chromatography.

analysis of **6e** (ESI†). All three newly formed chiral centers possess the *R* configuration. It is worth pointing out that the nitro group lies *anti* to the aryl group, occupying the less sterically hindered position. This supports the proposed epimerization of the center α to the nitro group towards the thermodynamically more stable product.

In summary, we have succeeded in developing a cascade reaction combining a catalytic oxidation with an organocatalytic enantioselective domino process. For a complex one pot reaction sequence we chose a prolinol catalyzed iminium–allenamine cascade as an example since it would be a good demonstration for the viability of this combined process.

We were able to show for the first time that the use of substrate-selective TPAP/NMO redox system is not only compatible with diarylprolinolsilyl ether catalysts, but also with different reactive functionalities and sensitive intermediates and chromene products. Thus, the *in situ* formed propargyl aldehydes could be further elaborated in the enantioselective domino process. The oxidative cycle in this combined catalytic procedure prevents the necessary purification or distillation step associated with the use of aldehydes in organocatalysis and should in particular be useful for reactions involving sensitive aldehydes as substrates. Hence, the reported procedure represents a valuable alternative to previously described procedures which do employ aldehydes and stoichiometric amounts of oxidants such as IBX or DDQ.

Important 4*H*-chromene derivatives could be synthesized by this operationally simple cascade, under mild conditions, in good yields and with excellent enantioselectivities. By applying a subsequent domino iminium–enamine cascade, we were able to prepare new complex tricyclic 4*H*-chromenes. In this sequential cascade, four bonds were formed and three chiral centers were controlled, yielding highly functionalized structures from simple starting materials (*i.e.* a propargyl alcohol, a cinnamaldehyde and a nitrostyrene derivative). This first unification of metal catalyzed oxidation with organocatalysis expands the scope of asymmetric covalent catalysis and combined catalytic procedures and we are confident that future developments will soon arise.

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Notes and references

1 Reviews: (*a*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*b*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638–4660; (*c*) A. N. Alba, X. Companyo, M. Viciano and R. Rios, *Curr. Org. Chem.*, 2009, **13**, 1432–1474; (*d*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167–178.

2 Review on tandem oxidation processes: (*a*) R. J. K. Taylor, M. Reid, J. Foot and S. A. Raw, *Acc. Chem. Res.*, 2005, **38**, 851–869; Selected examples of tandem oxidation processes: (*b*) M. F. Oswald, S. A. Raw and R. J. K. Taylor, *Org. Lett.*, 2004, **6**, 3997–4000; (*c*) S. A. Raw, C. D. Wilfred and R. J. K. Taylor, *Org. Biomol. Chem.*, 2004, **2**, 788–796; (*d*) M. F. Oswald, S. A. Raw and R. J. K. Taylor, *Chem. Commun.*, 2005, 2253–2255; (*e*) T. Ngouansavanh and J. Zhu, *Angew. Chem., Int. Ed.*, 2006, **45**, 3495–3497; (*f*) B. E. Maki, A. Chan, E. M. Phillips and K. A. Scheidt, *Org. Lett.*, 2007, **9**, 371–374; (*g*) M. I. Hall, S. J. Pridmore and J. M. J. Williams, *Adv. Synth. Catal.*, 2008, **350**, 1975–1978; (*h*) B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2008, **10**, 4331–4334; (*i*) K. Zeitler and C. A. Rose, *J. Org. Chem.*, 2009, **74**, 1759–1762; (*j*) H. Kim, Y. Park, J. Hong, H. Kim, Y. Park and J. Hong, *Angew. Chem., Int. Ed.*, 2009, **48**, 7577–7581; (*k*) M. Davi and H. Lebel, *Org. Lett.*, 2009, **11**, 41–44; (*l*) J. Brioche, G. Masson and J. Zhu, *Org. Lett.*, 2010, **12**, 1432–1435; (*m*) S. De Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190–1191; (*n*) S. De Sarkar and A. Studer, *Org. Lett.*, 2010, **12**, 1992–1995; (*o*) S. De Sarkar and A. Studer, *Angew. Chem., Int. Ed.*, 2010, **49**, 9266–9269; (*p*) C. A. Rose and K. Zeitler, *Org. Lett.*, 2010, **12**, 4552–4555; (*q*) J. H. Park, S. V. Bhilare and S. W. Youn, *Org. Lett.*, 2011, **13**, 2228–2231; (*r*) B. E. Maki, E. V. Patterson, C. J. Cramer and K. A. Scheidt, *Org. Lett.*, 2011, **13**, 3942–3945; (*s*) M. Rueping, H. Sundén, L. Hubener and E. Sugiono, *Chem. Commun.*, 2012, **48**, 2201–2203.

3 A. Quintard, A. Alexakis and C. Mazet, *Angew. Chem., Int. Ed.*, 2011, **50**, 2354–2358.

4 (*a*) Y. Hayashi, T. Itoh and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2011, **50**, 3920–3924; (*b*) S.-L. Zhang, H.-X. Xie, J. Zhu, H. Li, X.-S. Zhang, J. Li and W. Wang, *Nat. Commun.*, 2011, **2**, 211.

5 For the activation of propargyl aldehydes: (*a*) S. B. Jones, B. Simmons and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 13606–13607; (*b*) R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz and D. W. C. MacMillan, *Chem. Sci.*, 2011, **2**, 308–311.

6 (*a*) X. Zhang, S. Zhang and W. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 1481–1484; (*b*) C. Liu, X. Zhang, R. Wang and W. Wang, *Org. Lett.*, 2010, **12**, 4948–4951; (*c*) J. Alemán, A. Núñez, L. Marzo, V. Marcos, C. Alvarado and J. L. García Ruano, *Chem.–Eur. J.*, 2010, **16**, 9453–9456.

7 S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639–666.

8 (*a*) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 794–797; (*b*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212–4215; Reviews on prolinol TMS-ether catalysis: (*c*) C. Palomo and A. Mielgo, *Angew. Chem., Int. Ed.*, 2006, **45**, 7876–7880; (*d*) A. Mielgo and C. Palomo, *Chem.–Asian. J.*, 2008, **3**, 922–948.

9 For a review, see: B. A. Keay and P. W. Dibble, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Oxford, Pergamon, 1996, vol. 2, pp. 395–436.

10 Reviews on organcatalytic synthesis of biologically active molecules: (*a*) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138–1167; (*b*) R. M. de Figueiredo and M. Christmann, *Eur. J. Org. Chem.*, 2007, 2575–2600.

11 (*a*) M. Rueping, E. Sugiono and E. Merino, *Angew. Chem., Int. Ed.*, 2008, **47**, 3046–3049; (*b*) M. Rueping, E. Sugiono and E. Merino, *Chem.–Eur. J.*, 2008, **14**, 6329–6332; (*c*) M. Rueping, E. Merino and E. Sugiono, *Adv. Synth. Catal.*, 2008, **350**, 2127–2131; (*d*) M. Rueping, U. Uria, M.-Y. Lin and I. Atodiresei, *J. Am. Chem. Soc.*, 2011, **133**, 3732–3735; (*e*) M. Rueping and M.-Y. Lin, *Chem.–Eur. J.*, 2010, **16**, 4169–4172.

12 (*a*) H. Gotoh, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2007, **9**, 5307–5309; (*b*) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente and S. Vera, *Angew. Chem., Int. Ed.*, 2007, **46**, 8431–8435; (*c*) L. Zu, H. Xie, H. Li, J. Wang and W. Wang, *Adv. Synth. Catal.*, 2007, **349**, 2660–2664; (*d*) Y. Wang, P. Li, X. Liang, T. Y. Zhang and J. Ye, *Chem. Commun.*, 2008, 1232–1234.

13 For Michael/aldol condensation reaction from our group: (*a*) M. Rueping, A. Kuenkel, F. Tato and J. W. Bats, *Angew. Chem., Int. Ed.*, 2009, **48**, 3699–3702; (*b*) M. Rueping, A. Kuenkel and R. Fröhlich, *Chem.–Eur. J.*, 2010, **16**, 4173–4176.

14 Selected publications: (*a*) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863; (*b*) Z. Fang-Lin, A.-W. Xu, Y.-F. Gong, M.-H. Wei and X.-L. Yang, *Chem.–Eur. J.*, 2009, **15**, 6815–6818; (*c*) D. Enders, M. Jeanty and J. W. Bats, *Synlett*, 2009, 3175–3178; (*d*) P. Kotame, B.-C. Hong and J.-H. Liao, *Tetrahedron Lett.*, 2009, **50**, 704–707; (*e*) D. Enders, C. Wang, M. Mukanova and A. Greb, *Chem. Commun.*, 2010, **46**, 2447–2449; (*f*) B.-C. Hong, N. S. Dange, C.-S. Hsu and J.-H. Liao, *Org. Lett.*, 2010, **12**, 4812–4815; (*g*) B.-C. Hong, P. Kotame, C.-W. Tsai and J.-H. Liao, *Org. Lett.*, 2010, **12**, 776–779; (*h*) M. Rueping, K. Haack, W. Ieawsuwan, H. Sunden, M. Blanco and F. R. Schoepke, *Chem. Commun.*, 2011, **47**, 3828–3830.

