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Convergent Catalysis: Asymmetric Synthesis of Dihydroquinolines Using a Combined Metal Catalysis and Organocatalysis Approach

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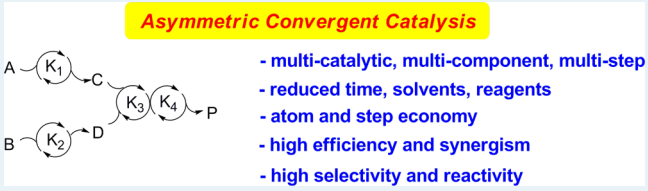
Supporting Information

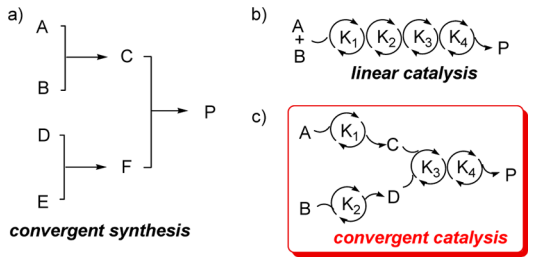
ABSTRACT: A convergent catalysis approach has been developed. The combined metal-catalyzed and organocatalyzed cascade consists of two oxidations, an aza-Michael addition and an aldol condensation, and involves a multicatalysis approach to provide 1,2-dihydroquinolines in a highly enantioselective fashion.



KEYWORDS: *domino reaction, diphenylprolinol ether, Michael reaction, TPAP oxidation, aldol reaction*

Convergent synthesis[1−4] is a versatile synthetic strategy that proved its strong potential in the synthesis of a large number of natural products and biologically active molecules.[5−10] In a convergent synthesis, fragments of the target molecule are synthesized independently and assembled together at various stages of the designed synthetic route to achieve a high degree of productivity (Scheme 1a). Compared to linear syntheses, convergent syntheses are usually more efficient in terms of the amounts of starting materials required and the number of reaction steps of the main route, being thus preferred in the synthesis of complex molecules.[1−10] One way to further enhance the efficiency of a convergent synthesis is to take advantage of domino, tandem, or sequential reactions and incorporate them in a more elaborate convergent strategy. Domino reactions[11−26] have attracted an increasing level of interest in organic synthesis because of their ability to create numerous bonds, via one-pot multistep processes, starting from simple, readily available materials (Scheme 1b). These atom-economical reactions represent a powerful tool for accessing complex structures with a great level of stereocontrol. Furthermore, they avoid laborious protection/deprotection steps as well as additional workup and purification strategies. Hence, merging the concepts of domino reactions and convergent synthesis should bring significant additional benefits in terms of yield as well as reaction time (Scheme 1c). Among the well-established domino reactions, chiral secondary amine-catalyzed[27,28] enantioselective organocascades emerged as a practical method for the functionalization of α,β-unsaturated aldehydes via iminium/enamine (Im/En) activation. In our previous investigations in the field of organocatalyzed cascade reactions, we observed that traces of acid impurities present in the α,β-unsaturated aldehydes are detrimental to the enantioselectivity.[29−31]

Scheme 1. Schematic Representation for (a) Convergent Synthesis, (b) Domino Reactions, and (c) Merged Convergent Synthesis and Domino Reactions



To avoid extra purification steps, we anticipate that *in situ* generation of the aldehydes by metal-catalyzed oxidation of alcohols would be advantageous.[32−48] Such an oxidative process could extend the versatility of Im/En cascades, especially when the aldehydes are unstable or difficult to access.[49−53] So far, to the best of our knowledge, there is no example in which both substrates of an Im/En cascade are generated *in situ*. Hence, we became interested in designing a novel convergent enantioselective cascade that would allow simultaneous conversion of the appropriate alcohols into the corresponding carbonyl compounds, which would subsequently react together in a secondary amine catalytic cycle.

Following this idea, we turned our attention to the Michael/intramolecular aldol reaction between α,β-unsaturated aldehydes and benzaldehydes. Indeed, these two starting materials could in principle be generated *in situ* by oxidation of the corresponding allylic and benzyl alcohols. Interestingly, in recent years, several elegant secondary amine-catalyzed domino hetero-Michael/aldol/dehydration reactions[54] were applied to the asymmetric preparation of valuable heterocycles such as chromenes,[53,55−59] thiochromenes,[60−62] or 1,2-dihydroquinolines.[63−65] We herein report an unprecedented convergent oxidative iminium/enamine cascade between 2-amino benzyl

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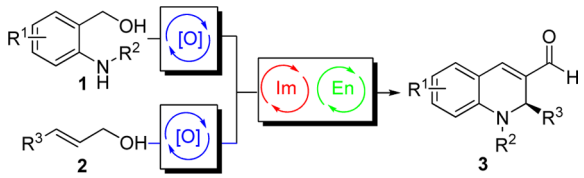
alcohols **1** and allylic alcohols **2** yielding 1,2-dihydroquinolines **3** (Scheme 2).[63−73] This class of heterocycles remains highly important as they are found in a number of natural and synthetic active molecules.[74]

Scheme 2. Double Oxidative Iminium/Enamine Cascade Reaction



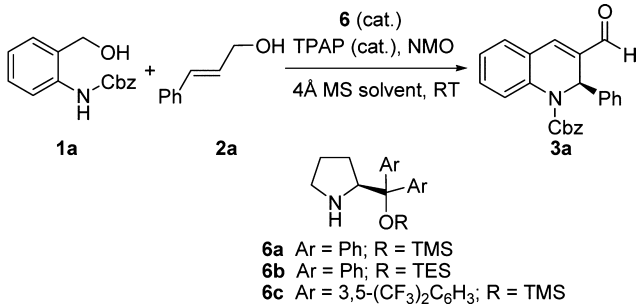
To our delight, during the initial investigations, we found that the catalytic oxidative system tetrapropylammonium perruthenate (TPAP),[75] associated with the mild terminal oxidant *N*-methylmorpholine *N*-oxide (NMO), could be combined in one pot with secondary amine-type catalysts.[76−81]

Thus, the TPAP/NMO system became the oxidant of choice for the convergent enantioselective domino process presented here. Both allylic and benzyl alcohols could be oxidized at room temperature under mild conditions, suitable for secondary amine catalysis.

As proposed in Scheme 3, initial oxidation of allylic alcohol **1** by the TPAP/NMO system provides the *α,β*-unsaturated aldehyde **4**, releasing *N*-methylmorpholine (NMM). The aldehyde is then activated in the form of iminium ion **A** by condensation with the diarylprolinol ether catalyst **6**.[82−84] Michael addition of 2-*N*-protected benzaldehyde **5**, formed by *in situ* oxidation of the corresponding 2-amino benzyl alcohol **2**, yields enamine **B**.[85] Intramolecular aldol reaction followed by dehydration leads to 1,2-dihydroquinoline **3** and the release of catalyst **6**.

To test the feasibility of our proposed enantioselective oxidative cascade, we first reacted *N*-Cbz-2-aminobenzyl alcohol **1a** with 2 equiv of cinnamyl alcohol **2a**, the TPAP (7 mol %)/NMO (3.5 equiv) system, and diarylprolinol TMS ether catalyst **6a** in CH_2Cl_2 at room temperature. After 48 h, the desired 1,2-dihydroquinoline **3a** was isolated in a promising yield (47%) and with very good enantioselectivity [93% enantiomeric excess (ee) (Table 1, entry 1)]. The absolute configuration was assigned to be *R* by comparing the sign of the optical rotation of the product with that of the known compound from the literature.[63] Use of 4 Å molecular sieves proved to be beneficial for the yield and slightly increased the enantioselectivity (62% yield, 95% ee, entry 2). A reversal of the reagent ratio and the use of 4 Å molecular sieves increased the yield to 72% and produced an excellent enantioselectivity (95% ee, entry 3). Molecular sieves, known to enhance the efficiency of TPAP/NMO oxidations, probably promoted the elimination step as well. When screening the catalysts, we observed that the TES-protected catalyst **6b** provided the desired product in a similar good yield, whereas organocatalyst **6c** was detrimental to enantioselectivity (entries 4 and 5). The effect of the solvent was subsequently evaluated with the initial catalyst **1a**. As seen

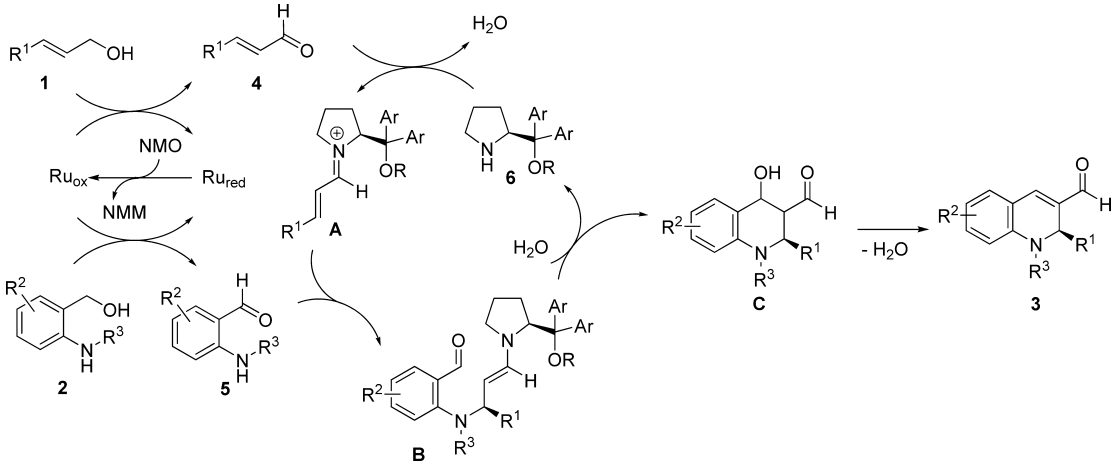
Table 1. Survey of the Reaction Conditions for the Convergent Enantioselective Oxidative Cascade Reaction



entry[a]	solvent	catalyst	yield (%)[b]	ee (%)[c]
1[d,e]	CH_2Cl_2	**6a**	47	93
2[e]	CH_2Cl_2	**6a**	62	95
3	CH_2Cl_2	**6a**	72	95
4	CH_2Cl_2	**6b**	73	95
5[f]	CH_2Cl_2	**6c**	<5	47
6	$Cl(CH_2)_2Cl$	**6a**	70	94
7	$CHCl_3$	**6a**	68	94
8	CH_3CN	**6a**	20	85
9	THF	**6a**	22	94

[a]Reaction conditions: 2:1 ratio of **1a** (2 equiv, 4 mmol) to **2a** (1 equiv, 1 mmol), TPAP (7 mol %), NMO (3.5 equiv), 4 Å molecular sieves (150 mg), and catalyst **6** (20 mol %) in solvent (2 mL) at room temperature for 48 h. [b]Yields after purification by column chromatography. [c]Determined by high-performance liquid chromatography (HPLC). [d]Without 4 Å molecular sieves. [e]A 1:2 ratio of **1a** (1 equiv) to **2a** (2 equiv) was used. [f]Reaction conducted for 120 h.

Scheme 3. Proposed Mechanism of the Convergent Oxidative Iminium/Enamine Cascade



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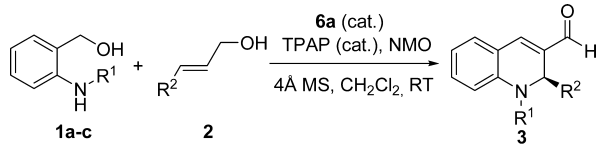
in entries 3, 6, and 7, chlorinated solvents such as dichloromethane, 1,2-dichloroethane [$Cl(CH_2)_2Cl$], and chloroform ($CHCl_3$) gave similar good results, whereas acetonitrile showed a poor efficiency and gave a lower enantioselectivity (entry 8). A polar solvent such as THF was also detrimental to the cascade reaction, and the desired product was isolated in 22% yield, although with 94% ee (entry 9).

With the optimized conditions in hand (Table 1, entry 3), the scope of the enantioselective oxidative cascade reaction was investigated.[86] The reaction between *N*-Cbz-protected amino alcohol **1a** and a variety of cinnamyl alcohols **2** afforded the desired 1,2-dihydroquinolines **3** in a highly enantioselective fashion (Table 2, entries 1−8).

Table 2. Scope of the Convergent Enantioselective Oxidative Cascade Reaction



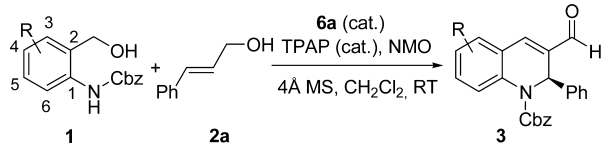
entry[a]	R^1	R^2	3	yield (%)[b]	ee (%)[c]
1	Cbz (**1a**)	Ph	**3a**	72	95
2	Cbz (**1a**)	4-NO_2-C_6H_4	**3b**	81	95
3	Cbz (**1a**)	4-Br-C_6H_4	**3c**	79	95
4	Cbz (**1a**)	4-F-C_6H_4	**3d**	71	92
5	Cbz (**1a**)	4-Me-C_6H_4	**3e**	69	94
6	Cbz (**1a**)	4-MeO-C_6H_4	**3f**	84	95
7	Cbz (**1a**)	3-MeO-C_6H_4	**3g**	73	96
8	Cbz (**1a**)	2-MeO-C_6H_4	**3h**	51	90
9[d]	Cbz (**1a**)	2-thienyl	**3i**	47	93
10[e,f]	Ac (**1b**)	Ph	**3j**	64	95
11[f]	Ts (**1c**)	Ph	**3k**	76	98
12[f]	Ts (**1c**)	4-MeO-C_6H_4	**3l**	85	91
13[g]	Ts (**1c**)	Me	**3m**	73	90
14[f,g]	Ts (**1c**)	*n*-Pr	**3n**	63	86
15[g]	Ts (**1c**)	$TBSOCH_2$	**3o**	61	87
16[f]	Ts (**1c**)	CO_2Et	**3p**	61	80

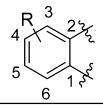
[a]Reaction conditions: 2:1 ratio of **1** (2 equiv) to **2** (1 equiv), TPAP (7 mol %), NMO (3.5 equiv), 4 Å molecular sieves, and catalyst **6a** (20 mol %) in CH_2Cl_2 at room temperature for 48 h. See the Supporting Information for details. [b]Yields after purification by column chromatography. [c]Determined by HPLC. [d]Reaction conducted for 120 h. [e]Reaction conducted for 84 h. [f]A 1:2 ratio of **1** (1 equiv) to **2** (2 equiv) was used. [g]Reaction conducted for 12 h.

A strong electron-withdrawing group such as a nitro group at the *para* position was compatible in the domino process, providing the product in 81% yield with excellent enantioselectivity (95% ee, entry 2). Halo-containing allylic alcohols were also subjected to this oxidative cascade, affording 4-bromo- and 4-fluorophenyl-substituted enantiopure products (entries 3 and 4). The electronic effect of the substituent was rather low as electron-rich 4-methoxyphenyl and 4-methylphenyl groups also displayed very good results in terms of yields and ee's (entries 5 and 6). However, the position of the methoxy substituent on the phenyl ring had an impact on the outcome of the reaction, as revealed by the *ortho*-, *meta*-, and *para*-substituted substrates (entries 6−8). Furthermore, the reaction tolerated a heteroaromatic 2-thienyl allylic alcohol, although a longer reaction time was required (entry 9). With regard to the *N*-protecting group, we found that in addition to Cbz, acetyl (Ac) and tosyl (Ts) groups are also compatible with the reaction (entries 10−12). *N*-Ts-protected amino alcohol **1c** turned out to be of interest as it allowed reaction with alkyl- and ester-substituted allylic alcohols, otherwise unreactive with the *N*-Cbz-protected substrate after 48 h (entries 13−16). Hence, (*E*)-crotyl alcohol and (*E*)-hex-2-en-1-ol were subjected to the oxidative domino process and afforded the corresponding 1,2-dihydroquinolines in good yields with good enantioselectivities (entries 13 and 14). In general, reactions with alkyl-substituted substrates were found to occur faster than with the corresponding aryl-substituted derivatives. Interestingly, silyl-protected hydroxymethyl and ester groups were also tolerated in the reaction and could be further functionalized, although the enantioselectivity was lower than for the aryl-substituted allylic alcohols (entries 15 and 16, ee's of 87 and 80%, respectively).

After varying the allylic alcohols **2** and the protecting group of the 2-aminobenzyl alcohol **1**, we evaluated the generality of our cascade by modifying the substitution on the aromatic ring of the latter. In this regard, several readily available Cbz-protected substrates were subjected to the domino cascade with cinnamyl alcohol **2a** (Table 3). Substrates bearing an electron-donating group [4-methyl, 4-methoxy, or 4,5-(OCH_2O)] provided very good results in terms of yields and ee's (entries 1−3). Halo-containing aminobenzyl alcohols were compatible in this oxidative cascade, affording the desired products with very high enantioselectivity (entries 4−6). We then tested the effect of the substituent *ortho* to the amino function. Pleasingly, *ortho* methyl functionality provided a good yield and an excellent ee (entry 7). Interestingly, a naphthalene derivative reacted smoothly to provide the corresponding product in acceptable yield with an excellent enantioselectivity (99% ee, entry 8).

Table 3. Extended Scope of the Convergent Enantioselective Oxidative Cascade Reaction



Entry[a]		3	Yield [%][b]	*ee* [%][c]
1	4-Me-C_6H_3	**3q**	70	95
2	4-OMe-C_6H_3	**3r**	67	95
3	4,5-(OCH_2O)-C_6H_2	**3s**	71	92
4	4-Br-C_6H_3	**3t**	80	95
5	5-Cl-C_6H_3	**3u**	72	91
6	5-CF_3-C_6H_3	**3v**	63	95
7	6-Me-C_6H_3	**3w**	63	99
8[d]	naphthyl	**3x**	43	99

[a]Reaction conditions: 2:1 ratio of **1** (2 equiv) to **2** (1 equiv), TPAP (7 mol %), NMO (3.5 equiv), 4 Å molecular sieves, and catalyst **6a** (20 mol %) in CH_2Cl_2 at room temperature for 48 h. See the Supporting Information for details. [b]Yields after purification by column chromatography. [c]Determined by HPLC. [d]Reaction conducted for 120 h.

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In conclusion, we have developed a new convergent catalysis approach by combining two catalytic oxidative cycles in one pot with iminium/enamine catalysis. The convergence of this process is caused by the oxidation of two substrates, an allylic alcohol and a 2-amino benzyl alcohol, by the substrate-selective redox TPAP/NMO system. This catalytic oxidation, compatible with diarylprolinolsilyl ether catalysis, allows the *in situ* generation of two aldehydes that react subsequently in an enantioselective Michael addition/intramolecular aldol/dehydration pathway. The domino reaction proved to be very efficient and general, affording a wide range of enantiopure *N*-protected 1,2-dihydroquinolines under mild and operationally simple conditions. This original process widens the scope of secondary amine catalysis as alcohols can now be used as starting materials instead of more sensitive aldehydes. Furthermore, our oxidative iminium/enamine cascade enhances the versatility of asymmetric covalent catalysis by exploiting the compatibility of metal catalysis with organocatalysis. Finally, the demonstrated convergent catalysis concept will be a blue print for many possible reaction combinations involving one-pot multicomponent multicatalysis.

■ ASSOCIATED CONTENT

Supporting Information

General procedures, full characterization of the products, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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