Asymmetric Catalysis

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Dihydropyridones: Catalytic Asymmetric Synthesis, N- to C-Sulfonyl Transfer, and Derivatizations**

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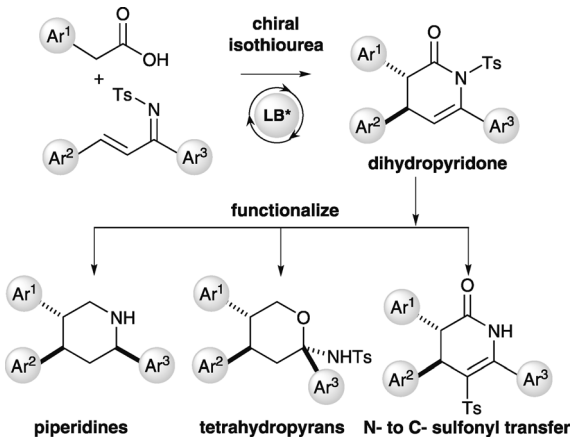
The piperidine and dihydropyridone motifs are a recognized feature of numerous structurally diverse natural products and bioactive pharmaceuticals.[1] Among the synthetic methods developed for the preparation of these derivatives in enantiomerically pure form,[2] the aza-Diels–Alder reaction is an important and versatile route.[3] Since the introduction of uncatalyzed inverse-electron-demand aza-Diels–Alder cycloaddition processes by Boger and Kasper,[4] and Hsung and Berry,[5] few catalytic asymmetric methods for the promotion of this reaction have been developed.[6,7] The state-of-the-art N-heterocyclic carbene promoted[8] organocatalytic methods of Bode and co-workers (using enals and *N*-sulfonyl-α,β-unsaturated aldimines),[9] and those of Ye and co-workers (arylalkylketenes and *N*-sulfonyl butenoates)[10] furnish dihydropyridones with high diastereo- and enantioselectivity; on the otherhand Chen and co-workers have employed enamine[11] and dienamine[12] catalysis in the transformation of *N*-sulfonyl-α,β-unsaturated ketimines[13] into pyridinols with high enantioselectivity. To date, processes that utilize enolate equivalents that have been prepared directly from readily available and bench-stable carboxylic acids have not been developed.[14]

Within this area, Romo and co-workers,[15] and ourselves[16] have utilized Lewis base catalyzed[17] in situ activation of a carboxylic acid,[18] in combination with chiral isothioureas[19] (introduced as acyl transfer catalysts by Birman et al.),[20] to promote asymmetric aldol- and Michael/lactonization processes, respectively. To date, the only intermolecular process using this strategy requires α-keto-β,γ-unsaturated esters as the Michael acceptor, with chalcones being unreactive. To build upon this work, we envisaged that the electron-withdrawing *N*-sulfonyl group within *N*-tosyl-α,β-unsaturated ketimine derivatives would facilitate intermolecular organocatalytic Michael/lactamization, furnishing directly stereodefined dihydropyridones from arylacetic acids under isothiourea-mediated catalysis. We detail herein our studies toward this goal, as well as a range of derivatization procedures and a new N- to C-sulfonyl photoisomerization process, for the efficient asymmetric synthesis of polysubstituted dihydropyridones, dihydropyridines, piperidines, and tetrahydropyrans with high stereocontrol (Scheme 1).

Initial investigations probed the viability of this Michael/lactamization sequence using phenylacetic acid (**1**) and ketimine **2** (Table 1). Initial screening of a number of



Scheme 1. Versatile route to N- and O-heterocyclic building blocks. Ts = *p*-toluenesulfonyl, LB = Lewis base.

isothioureas showed that benzotetramisole (**4**)[21] was a competent catalyst for this transformation,[22] thus giving **3** with promising diastereo- and enantioselectivity (entry 1; 92:8 d.r., 71% *ee*).[23] Using an excess (2 equivalents) of phenylacetic acid (**1**) gave higher yield of isolated product, whereas lowering the reaction temperature led to higher enantioselectivity, but modest conversion into product (entries 2–4). Switching the solvent from CH_2Cl_2 to THF led to increased yield and enantioselectivity, with good reaction conversion within 2 hours at room temperature (entry 5; 88:12 d.r., 96% *ee*). The reduction of catalyst loading to 5 mol% had a detrimental effect on product yield and *ee* value (entries 5–7). An investigation of different activating groups and the order of addition of the reagents led to improved enantioselectivity;[24] although the use of TsCl or $(4\text{-}MeOC_4H_6CO)_2O$ led to good yield and enantioselectivity (entries 8 and 9), the use of pivaloyl chloride led to optimal enantioselectivity and gave **3** in 79% yield after 2 hours at room temperature (entry 10).[25]

Subsequent studies probed the generality of this Michael addition/lactamization process, with initial work focusing upon variation of the arylacetic acid component, with **2** as the standard ketimine (Scheme 2).[26] Under the optimized reaction conditions this process readily accommodates substitution at the 2-, 3- and/or 4-position of the aryl unit with

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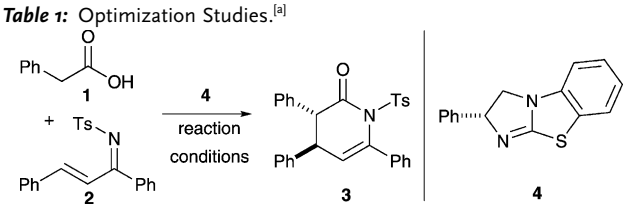
Table 1: Optimization Studies.[a]



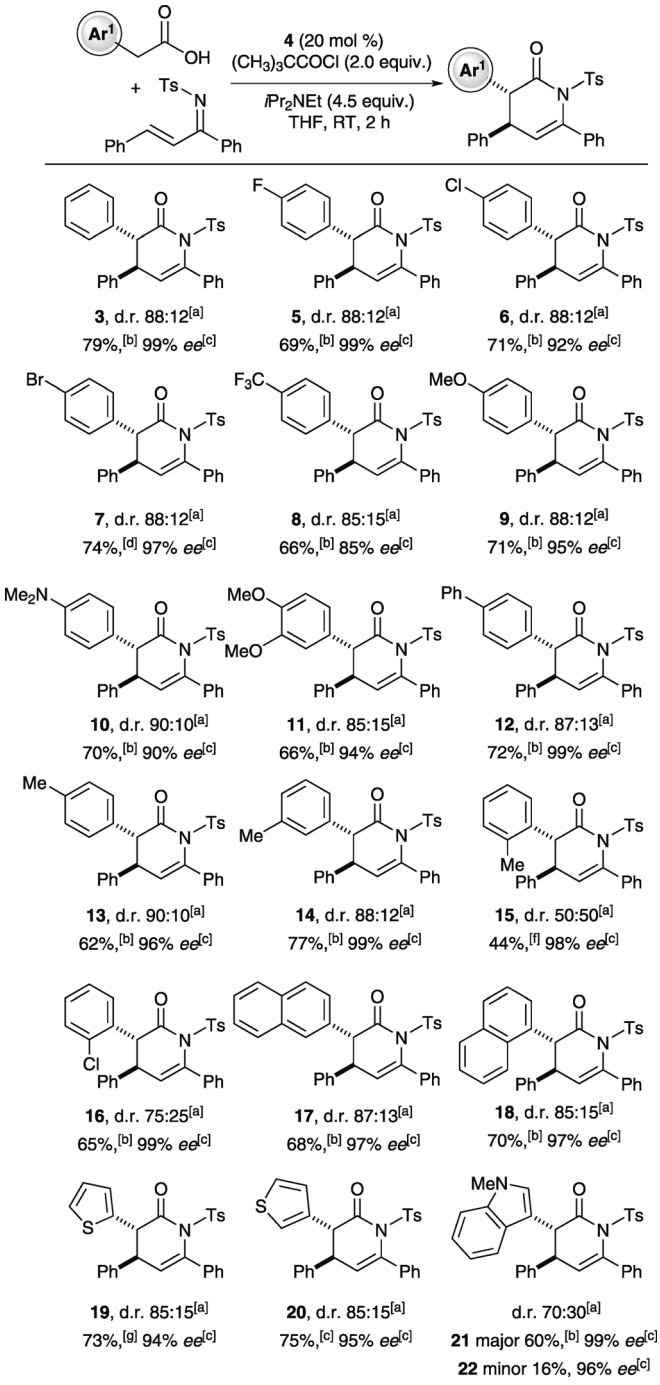
Entry	**4** (mol%)	*T* [°C]	Activating agent	d.r.[b]	Yield[c]	*ee* [%][d]
1[e,f]	20	RT	$(CH_3)_3CCOCl$	92:8	61	71
2[e,f]	20	RT	$(CH_3)_3CCOCl$	90:10	66[g]	77
3[e,f]	20	0	$(CH_3)_3CCOCl$	89:11	52[g]	76
4[e,f]	20	−78	$(CH_3)_3CCOCl$	83:17	33[g]	94
5[f,h]	20	RT	$(CH_3)_3CCOCl$	88:12	79[g]	96
6[f,h]	10	RT	$(CH_3)_3CCOCl$	88:12	51[g]	79
7[f,h]	5	RT	$(CH_3)_3CCOCl$	88:12	46[g]	77
8[h,i]	20	RT	TsCl	92:8	75[g]	94
9[h,i]	20	RT	$(4\text{-}MeOC_6H_4CO)_2O$	90:10	81[g]	91
10[h,i]	20	RT	$(CH_3)_3CCOCl$	88:12	79[g]	99

[a] Reaction Conditions: Benzotetramisole (**4**; 5–20 mol%), activating agent (up to 2 equiv.), iPr$_2$NEt (up to 4.5 equiv.), solvent, *T*. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Yield of isolated major diastereoisomer of **3** (d.r. ≥ 95:5). [d] Determined by HPLC analysis. [e] Solvent CH_2Cl_2. [f] Benzotetramisole (**4**) added to mixture of acid **1**, ketimine **2**, activating agent and base. [g] 2 equivalents of acid were used. [h] Solvent THF. [i] Ketimine **2** and benzotetramisole (**4**) added to a mixture of acid **1**, activating agent and base.

electron-withdrawing and electron-donating substituents, as well as with heteroaryl substituents. Notably, the presence of an electron-withdrawing 4-$CF_3C_6H_4$ substituent led to reduced product enantioselectivity (product **8**, 85% *ee*).[27] Reduced product diastereoselectivity was observed with 2-tolyl, 2-chloro or *N*-Me-3-indole substitution (products **15**,[28] **16**, **21**, and **22**), although the *anti* diastereoisomer was isolated with high *ee* values in each case (up to 99% *ee*). Also noteworthy is that this Michael/lactamization sequence was carried out on a preparative scale, with the reaction of phenylacetic acid (**1**) and ketimine **2** on a 4.15 mmol scale giving approximately 1.5 g of dihydropyridone **3** (88:12 d.r.; after chromatography: 71% yield, 98:2 d.r., and 94% *ee*).

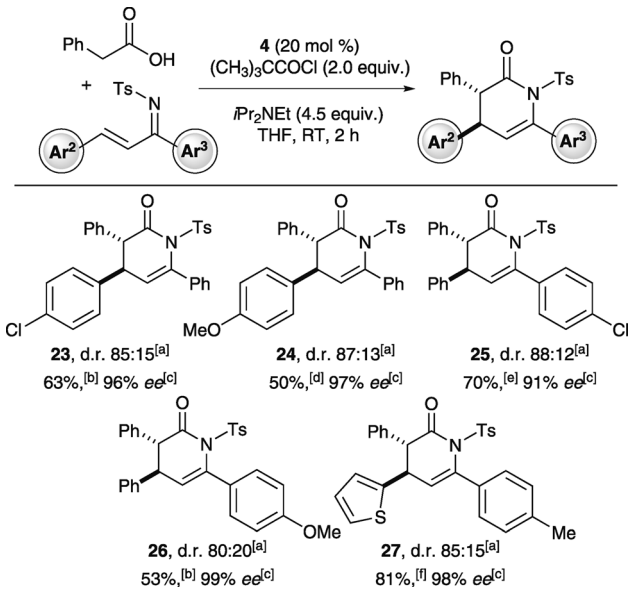
The treatment of phenylacetic acid with a number of *N*-tosyl-α,β-unsaturated ketimines[29] was then explored (Scheme 3). For the ketimine, aryl units containing electron-donating or electron-withdrawing substitutents at C(1) and C(3), as well as heteroaryl substitution at C(3), are readily tolerated, thus giving preferentially the corresponding *anti* dihydropyridones **23**–**27** in excellent enantioselectivity (up to 99% *ee*).

We postulate that the catalytic cycle for these transformations proceeds through the initial formation of the mixed anhydride from the arylacetic acid and pivaloyl chloride, followed by formation of the corresponding acyl ammonium ion. Deprotonation of the acyl ammonium ion will generate the *Z* enolate, which then undergoes stereoselective Michael addition, followed by intramolecular cyclization, to generate the corresponding dihydropyridone (Scheme 4).

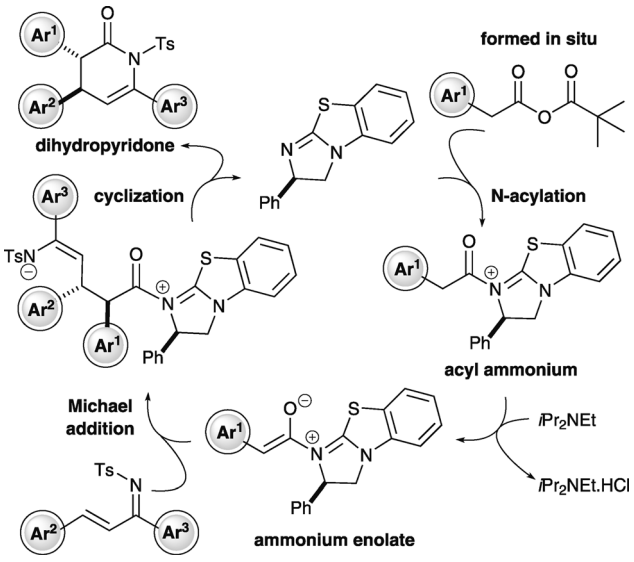


Scheme 2. Variation of the acid component. [a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Yield of isolated product (≥ 95:5 d.r.). [c] Determined by HPLC analysis. [d] Yield of isolated **7** (d.r. 93:7). [e] Yield of isolated **12** (d.r. 89:11). [f] Yield of isolated **15** (d.r. 94:6). [g] Yield of isolated **19** (d.r. 92:8).

A series of simple but versatile derivatizations were next examined to showcase the utility of these products as building blocks in synthesis. Interestingly, upon prolonged storage, these dihydropyridones, such as **17**, undergo isomerization to the corresponding C(5)-sulfonyl products, such as **28** (isolated as a single diastereoisomer), without significant loss of enantiopurity (Scheme 5).[30] This sulfonyl transfer also

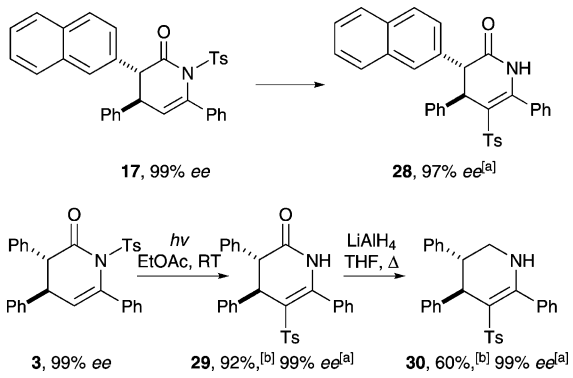


Scheme 3. Variation of the ketimine component. [a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Yield of isolated major diastereoisomer (d.r. 98:2) unless otherwise stated. [c] Determined by HPLC analysis. [d] Yield of isolated **24** (d.r. 93:7). [e] Yield of isolated **25** (d.r. 94:6). [f] Yield of isolated **27** (d.r. 88:12).



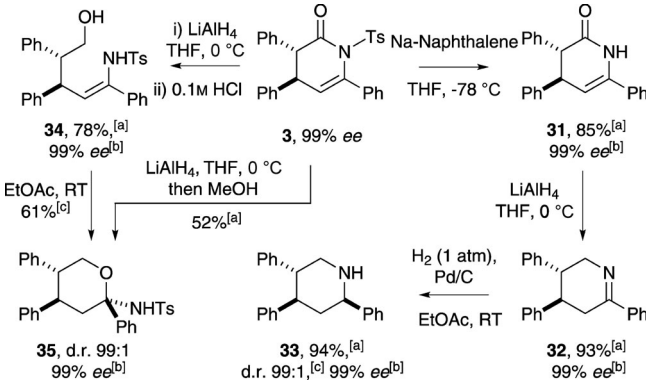
Scheme 4. Proposed mechanism of dihydropyridone formation

occurs upon heating in EtOAc, with **3** being converted into **29** (61% yield) over 72 hours.[31] However, efficient N- to C-sulfonyl transfer was achieved quantitatively through photoisomerization,[32] generating *C*-sulfonyl **29** (92% yield, 99% *ee*), which can be readily reduced with $LiAlH_4$ to generate dihydropyridine **30** in 60% yield and 99% *ee*.[33] Whereas photochemically promoted N- to C-sulfonyl transfer of sulfonamides,[34] sulfonylureas,[35] and sulfonyloxypyrimidines,[36] which often lead to product mixtures have been reported,[37] to the best of our knowledge this is the first selective example of an N- to C-sulfonyl photoisomerization reaction of dihydropyridones.



Scheme 5. N- to C-sulfonyl transfer of dihydropyridones. [a] Determined by HPLC analysis. [b] Yield of isolated product (d.r. 99:1).

Alternatively, N-deprotection and reduction of **3** (d.r. 98:2, 99% *ee*) was readily achieved through sequential removal of the N-tosyl group,[38] $LiAlH_4$ reduction, and hydrogenation to give piperidine **33** as a single diastereoisomer in 99% ee[39] and 74% overall yield over three steps (Scheme 6). Further investigation showed that reduction of **3**



Scheme 6. Derivatization and functionalization of **3**. [a] Yield of isolated product. [b] Determined by HPLC analysis. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product.

(98:2 d.r., 99% *ee*) with $LiAlH_4$, followed by addition of either aqueous HCl or MeOH, gave enamide **34** (78% yield and 99% *ee*) or amino lactol **35**[40] containing a quaternary stereogenic center as a single diastereoisomer (52% yield, 99% *ee*), respectively.[41] Enamide **34** can be converted into **35** (d.r. 99:1) simply by stirring in EtOAc at room temperature.

To conclude, benzotetramisole mediates the transformation of a range of arylacetic acids and *N*-tosyl-α,β-unsaturated ketimines into dihydropyridones with high diastereo- and enantiocontrol (up to 90:10 d.r., 99% *ee*) by an asymmetric Michael/lactamization process. The dihydropyridone products undergo efficient N- to C-sulfonyl photoisomerization, and are readily derivatized to a range of stereodefined synthetic building blocks. Current research is directed toward the development of alternative uses of isothioureas and other Lewis bases in asymmetric catalysis.

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[22] See the Supporting Information for full catalyst screening results.
[23] Racemic (±)-**3** was prepared using the achiral isothiourea DHPB (3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole), giving (±)-**3** (87:13 d.r.) in 66% yield upon isolation (98:2 d.r. after purification). Racemic samples of all products for unambiguous HPLC analysis were subsequently made using DHPB as a catalyst.
[24] In the absence of the isothiourea catalyst a significant (presumably base-promoted) background reaction is observed with pivaloyl chloride, giving (±)-**3** in 25% yield (87:13 d.r.). Minimization of this competitive background reaction leads to improved enantioselectivity and can be achieved with dropwise-addition of the isothiourea and ketimine to a solution of the preformed mixed anhydride (from phenylacetic acid and pivaloyl chloride). This optimized process can lead to dramatically improved enantioselectivities in some cases; for example, see: Ref. [27].
[25] The relative and absolute configuration of **3** was assigned by analogy to the absolute configurations of **28** and **35**, which were assigned by X-ray crystal structure analyses; all other derivatives were assigned by analogy. See Refs. [30] and [40] for further information.
[26] At the moment this process is limited to arylacetic acid derivatives; for example the use of trifluoropropionic acid or 2-nitroacetic acid under standardized reaction conditions returned only starting material. Current investigations are underway to further the scope of this process.
[27] We postulate that this reduced *ee* value may be due to a competitive racemic background reaction as mentioned in Ref. [24]. Under optimized conditions **8** was obtained with an *ee* value of 85%; without using this dropwise-addition process an *ee* value of 39% was obtained (d.r. 94:6, 79% yield).
[28] Transformation of 2-tolylacetic acid gave, following purification, **15** in a 50:50 d.r. (44% yield, 98% *ee*). The *anti* isomer of **15** was assigned on the basis of coupling constant analysis ($J_{C(3)H-C(4)H}$ = 11.3 Hz; the typical $J_{C(3)H-C(4)H}$ value for the *anti* diasteromer of most examples in this manuscript is 10–12 Hz). The *syn* diastereoisomer was isolated, although contaminated with an unknown impurity, and showed a characteristic smaller coupling constant ($J_{C(3)H-C(4)H}$ = 6.0 Hz). See the Supporting Information for further information.
[29] See the Supporting Information for the preparation of *N*-tosyl-α,β-unsaturated ketimines.
[30] The relative and absolute configuration of **28** was confirmed by X-ray crystal structure analysis. CCDC 851659 (**28**) contains 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.
[31] The relative configuration within **29** (CCDC 851660) was confirmed by X-ray crystal structure analysis. The bond connectivity and relative configuration of **29** was also confirmed through a combination of ^{15}N NMR spectroscopic investigations and coupling constant analysis. See the Supporting Information for further details.
[32] Photoisomerization of **3** (100 mg, 0.2 mM in EtOAc) was carried out at RT through pyrex and unfiltered light from 12xPhillips Cleo 15W UVA bulbs for 16 h was used.
[33] Treatment of **30** with Pd/C and H_2 (10 bar) resulted in hydrogenation and hydrogenolysis, giving piperidine **33** as a single diastereoisomer in quantitative yield.
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[38] The relative configuration of **31** (CCDC 851661) was confirmed by X-ray crystal structure analysis.
[39] The *ee* value of **33** was confirmed by HPLC analysis of the corresponding *N*-tosyl derivative **36**. The relative configuration of *N*-tosyl derivative **36** was also confirmed through NMR spectroscopic investigations using a combination of NOE and coupling constant analysis. See the Supporting Information for further details.
[40] The relative and absolute configuration of **35** (CCDC 851662) was confirmed by X-ray crystal structure analysis.
[41] Presumably **35** arises from the initial formation of **34**, followed by enamide to imine tautomerization and in situ cyclization. See the Supporting Information for a plausible stereochemical rationale for this transformation.

