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Efficient and Practical Ag-Catalyzed Cycloadditions between Arylimines and the Danishefsky Diene

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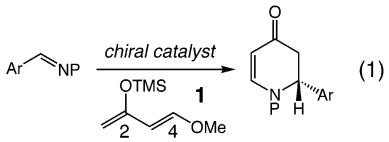
Danishefsky's diene (**1**) is a versatile reagent in chemical synthesis.[1] A set of transformations that involve the use of **1** is the Diels−Alder cycloaddition with imines (eq 1);[2] these reactions deliver chiral N-containing heterocycles that can be converted to functionalized piperidines. Several catalytic enantioselective variants of the above process have been reported.[3] These protocols often require up to 20−40 mol % catalyst and only afford appreciable selectivities (usually <90% ee) when specific structural requirements are met.[3a,b] Cycloadditions promoted by low catalyst loadings (1 mol %) are available when strongly electrophilic imines and fully functionalized derivatives of **1** are utilized (Me groups at C2 and C4).[3c]



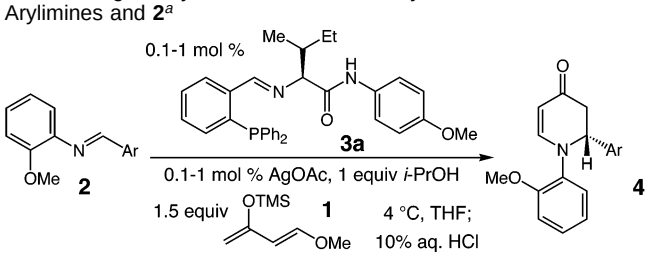
(1)

Herein we disclose an efficient Ag-catalyzed asymmetric addition of **1** to aryl imines to afford cycloadducts in >77% yield and >89% ee. Reactions are effected in the presence of ≤1 mol % catalyst (4 °C). The chiral ligand is a phosphine prepared from an inexpensive amino acid and other commercially available materials.[4] Catalytic transformations can be carried out neat or with undistilled THF in air. A recyclable supported chiral catalyst is also described.

To identify optimal conditions, we probed the transformations of different imines derived from 2-naphthaldehyde (e.g., **2c**, Table 1). After it was established that the derived *o*-anisidyl imine undergoes Diels−Alder reactions most efficiently, parallel libraries[5] of amino acid-based ligands, metal salts, and additives were examined. These investigations led us to establish that treatment of **2a** with 1.5 equiv of diene **1**, 1 mol % **3a**, 1 mol % AgOAc, and 1 equiv of *i*-PrOH (THF, 4 °C) followed by HCl workup affords cycloadduct **4a** in 93% ee and 94% isolated yield. As the data in entry 2 of Table 1 indicate, the catalytic cycloaddition can be effected in 92% ee and yield with only 0.5 mol % loading. The reaction proceeds to >98% conv with 0.1 mol % of the chiral Ag complex (entry 3), albeit with diminished enantioselectivity (88% ee). Moreover, a range of arylimines, including sterically hindered (e.g., **2b**, entry 4) substrates or those that bear electron-donating (e.g., **2d** and **2f**) or electron-withdrawing substituents (e.g., **2g** and **2h**), can be employed to access the desired piperidines in ≥89% ee and ≥86% isolated yield.

Several additional points are noteworthy: (1) The presence of the *o*-OMe group in imine substrates is required for high enantioselectivity but not reactivity. For example, reaction of phenyl and *o*-tolyl derivatives of **4c** proceed to >90% conv under conditions shown in Table 1 but afford the cycloaddition product in only 35−40% ee. (2) In contrast to the previously reported catalytic asymmetric additions to imines,[6] dipeptide phosphines give significantly lower selectivity and efficiency levels. (3) In the absence of *i*-PrOH, significantly lower conversions and enantioselectivities are obtained. As an example, even with 10 mol % catalyst loading, addition of **1** to **2c** proceeds to only 30% conv after 24 h (4 °C) to provide **4c** in 43% ee (compare to entry 1, Table 1). Other proton sources such as *t*-BuOH, MeOH, or water (see Scheme 1) can be used as additives or cosolvents; in 1:1 THF:H_2O, formation of **4c** (91% ee) proceeds to >98% conv (5 mol % **3a**). (4) As shown in Scheme 1, cycloadditions can be carried out effectively in the absence of solvent with minor diminution in selectivity and yield. Although reactions in Table 1 are effected under N_2, as the examples in Scheme 1 indicate, asymmetric cycloadditions proceed in air and with undistilled commercial THF with high selectivity and yield. (5) During screening studies, we established that the steric and electronic properties of the amide terminus can have a notable effect on enantioselectivity or conversion. Representative data are shown in Table 2.

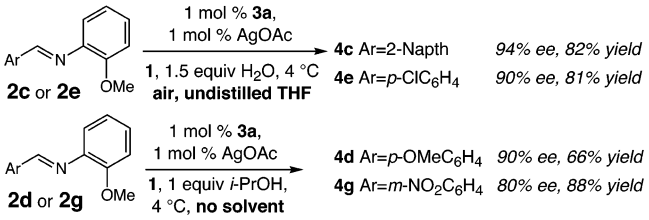
Table 1. Ag-Catalyzed Enantioselective Cycloaddition between Arylimines and **2**[a]



entry	Ar		**3a**, AgOAc (mol %)	yield (%)[b]	ee (%)[c]
1	Ph	**2a**	1.0	94	93
2	Ph	**2a**	0.5	92	92
3	Ph	**2a**	0.1	78	88
4	1-naphth	**2b**	1.0	94	90
5	2-naphth	**2c**	0.5	>98	95
6	*p*-OMe	**2d**	1.0	86	91
7	*p*-Cl	**2e**	1.0	98	90
8	*o*-Br	**2f**	1.0	91	89
9	*m*-NO_2	**2g**	1.0	92	91
10	*p*-NO_2	**2h**	1.0	>98	92
11	2-furyl	**2i**	1.0	89	92

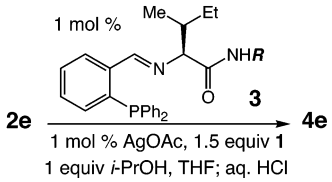
[a] Conditions: All reactions run under N_2 atm (12 h). [b] Isolated yields. [c] Determined by chiral HPLC (Chiralcel OJ for entries 1−3, 6−8; chiralcel OD for entries 4, 5, and 11 and chiralcel AD for entries 9 and 10).

Scheme 1. Catalytic Cycloadditions Performed without Solvent and in Air



10.1021/ja030033p CCC: $25.00

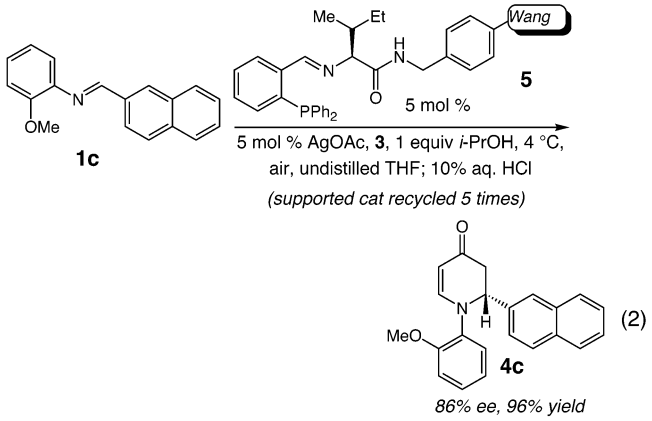
Table 2. Effect of Amide Moiety on Ag-Catalyzed Enantioselective Cycloadditions[a]



entry	R		conv (%)	ee (%)
1	*p*-OMeC$_6$H$_4$	**a**	>***98***	**92**
2	*p*-CF$_3$C$_6$H$_4$	**b**	75	88
3	2,6-Me$_2$C$_6$H$_3$	**c**	53	28
4	NHBu	**d**	>98	80
5	Bn	**e**	>98	80
6	NH(OMe)	**f**	52	20

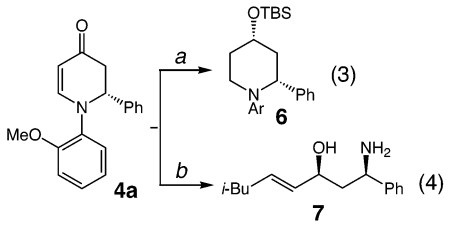
[a] See Table 1 for reaction conditions.

Because of the robustness of these asymmetric catalytic transformations and the significance of piperidines to biological chemistry, the availability of an effective supported ligand constitutes an important aspect of this research, particularly in relation to high throughput enantioselective synthesis. The data in eq 2 summarize results of our initial studies; ligand **5** can be reused through at least five cycles.[7] It should be noted that cycloadditions with **5** are performed in air and with undistilled THF (fresh AgOAc added for each cycle), and lower enantioselectivities are consistent with the data shown in entry 5 of Table 2 (**3e**, NHBn vs NAr terminus).



As the examples in eqs 3 and 4 illustrate, enantioenriched cyclic amines[8] can be functionalized diastereoselectively. Noteworthy is the rupture of the piperidine ring that occurs upon treatment of **4a** with the alkylcuprate[9] to afford the derived acyclic β-amino ketone (Mannich addition product). Subsequent stereoselective reduction[10] (10:1, syn:anti) and removal of the *o*-anisidyl group[11] delivers amino alcohol **7** (93% ee).

Future research will involve the development of catalytic asymmetric cycloadditions with aliphatic imines, processes which will likely involve in situ imine formation/cycloaddition[6e] and might require a different chiral ligand.[5c] Upcoming detailed mechanistic



a. 1. LAH (2 portions), THF, –78 °C; 68%, 9:1 syn:anti. 2. TBSCl, imid, DMF; 98% *b.* 1. *i*-BuMgCl, CuCN, $BF_3{\cdot}Et_2O$, THF; 96%. 2. $Zn(BH_4)_2$, THF. 3. $AgNO_3$, $(NH_4)_2S_2O_8$, MeCN, H_2O; 80% overall.

studies will include investigating the role of *i*-PrOH additive and whether it is involved in shuttling Me_3Si from O to N (or vice versa) and/or the release of Ag from product. These studies will explore the coordination geometry of the Ag center(s) by establishing the kinetic details of the catalytic cycle and the exact structure (stoichiometry) of the reactive substrate-catalyst complex.

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Supporting Information Available: Experimental procedures and spectral and analytical data for reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15−23.
(2) Kerwin, J. F.; Danishefsky, S. J. *Tetrahedron Lett.* **1982**, *23*, 3739−3742.
(3) (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979−981. (b) Kobayashi, S.; Kusakabe, K.; Kimoyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 5220−5221. (c) Yao, S.; Johannsen, M.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121−3124. For a noncatalytic enantioselective cycloaddition, see: (d) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264−3265.
(4) For previous reports regarding amino acid-based phosphine ligands, see: (a) Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522−6523. (b) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (c) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (d) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (e) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363. (f) Hird, A. W.; Hoveyda, A. H. *Agnew. Chem., Int. Ed.* In press. (g) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* In press.
(5) (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671. (b) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707. (c) Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; pp 991−1016.
(6) (a) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (b) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658. (c) Jospehsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599. (d) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. (e) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410.
(7) See the Supporting Information for results of recycling studies.
(8) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677−680.
(9) For conjugate additions to the corresponding carbamates (cyclic products obtained), see: Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997**, *62*, 8182−8187.
(10) Pilli, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1213−1214.
(11) Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett.* **1990**, 229−230.

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