J|A|C|S COMMUNICATIONS

Published on Web 05/04/2009

Amino-Indanol Catalyzed Enantioselective Reactions of 3-Hydroxy-2-Pyridones

Julian Ying-Teck Soh and Choon-Hong Tan*

Department of Chemistry, 3 Science Drive 3, National University of Singapore, Singapore 117543

Received January 24, 2009; E-mail: chmtanch@nus.edu.sg

The Diels−Alder reaction is one of the most important reactions for the synthesis of complex molecules, providing access to carbocyclic compounds containing up to four stereogenic centers in a single step.[1] Asymmetric catalysis in a Diels−Alder reaction has mainly been realized using chiral Lewis acids.[2] Recently, the use of organic Brønsted acids or Brønsted bases has emerged as a viable alternative for catalytic Diels−Alder reactions.[3] Cycloaddition of 2-pyrone and 2-pyridone dienes generates structurally and stereochemically rich bicyclooctenes. However, these dienes have some aromatic character and participate in Diels−Alder reactions less readily.[4] Deng et al. reported that 3-hydroxy-2-pyrones, using a cinchona alkaloid derivative as a catalyst, can take part in Diels−Alder reactions with excellent ee's.[5] Okamura et al. were the first to report that the Diels−Alder reactions of 3-hydroxy-2-pyridone can be catalyzed by Brønsted bases.[6] While preparing a glycosidase inhibitor, Vasella developed a methodology using quinine to promote the reaction between 3-hydroxy-2-pyridone and 8-phenylmenthyl acrylate, leading to a dr of 96%.[7]

Organic bifunctional catalysts possessing both hydrogen bond donor and acceptor moieties have been successful in many enantioselective reactions.[8] These catalysts are often derivatives of the cinchona alkaloids and/or contain urea/thiourea functionality.[9] We are keen to develop simple catalysts, such as simple amino-alcohols **1a**−**d** that empower such modes of interactions (Figure 1).

Preliminary studies showed that the reaction between **2a** and *N*-phenylmaleimide **3a** can be catalyzed by 10 mol % of amino-indanols **1a**−**d** (Table 1, entries 1−4). In all reactions, only a single diastereoisomer was obtained, the *endo*-adduct. Moderate enantioselectivities were obtained, with catalyst **1a** showing the most promising results. The *cis* relationship of the amino and alcohol functional groups in the amino-indanols was critical for obtaining good enantioselectivity. Chlorinated solvents such as CH_2Cl_2 and $CHCl_3$ gave the most desired results. When the reaction temperature was lowered to −50 °C, adduct **4a** was obtained with an ee of 93% (entry 5). Subsequently, a series of *N*-substituted pyridones including **2b**−**c** (entries 6−7) was prepared.[10] With the optimized conditions, both *N*-alkyl and *N*-aryl maleimides **3b**−**g** (entries 8−13) gave adducts with high ee's.

C4-Derivatives of 3-hydroxy-2-pyrones were prepared by Tsuboi and co-workers using a fairly extensive route,[11] while C4-derivatives of 3-hydroxy-2-pyridones were unknown. It was reported that 2-pyridone contains aromatic character,[4] so we hypothesize that it should undergo electrophilic substitution reactions similar to phenol.

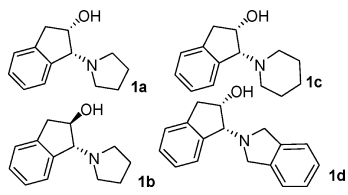
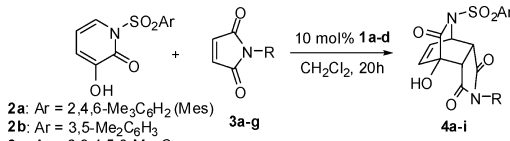


Figure 1. Amino-indanols.

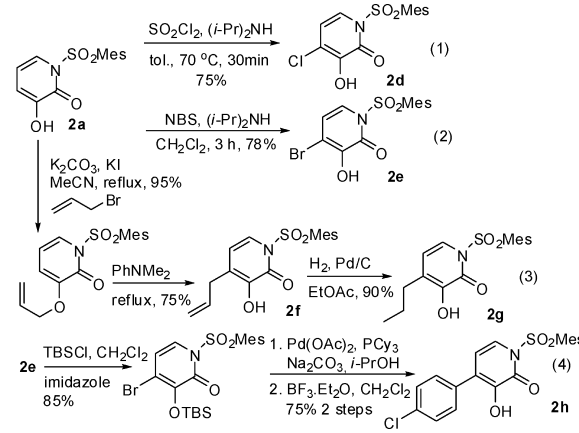
Table 1. Amino-Indanol Catalyzed Diels−Alder Reactions between *N*-Sulphonamide-3-hydroxy-2-pyridones **2a**−**c** and Maleimides **3a**−**g**



entry	catalyst	2	3 [R]	4	temp/°C	yield /%[a]	ee /%[b]
1	**1a**	**2a**	**3a** [Ph]	**4a**	rt	96	61
2	**1b**	**2a**	**3a** [Ph]	**4a**	rt	97	32
3	**1c**	**2a**	**3a** [Ph]	**4a**	rt	93	40
4	**1d**	**2a**	**3a** [Ph]	**4a**	rt	93	53
5	**1a**	**2a**	**3a** [Ph]	**4a**[c]	−50	93	93
6	**1a**	**2b**	**3a** [Ph]	**4b**	−50	96	81
7	**1a**	**2c**	**3a** [Ph]	**4c**	−50	96	88
8	**1a**	**2a**	**3b** [Et][d]	**4d**	−50	92	87
9	**1a**	**2a**	**3c** [Bn][d]	**4e**	−50	90	89
10	**1a**	**2a**	**3d** [4-$EtOC_6H_4$][d]	**4f**	−50	89	92
11	**1a**	**2a**	**3e** [3,4-$Cl_2C_6H_3$][d]	**4g**	−50	90	93
12	**1a**	**2a**	**3f** [4-BrC_6H_4][d]	**4h**	−50	92	94
13	**1a**	**2a**	**3g** [4-MeC_6H_4][d]	**4i**	−50	95	94

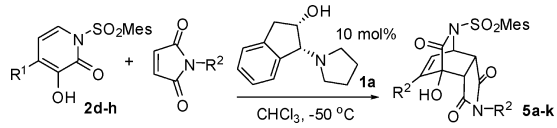
[a] Isolated yield. [b] Ee's were determined by chiral HPLC. [c] Absolute configuration of **4a** determined by X-ray analysis. [d] A solvent mixture of CH_2Cl_2 and PhCl (1:1) was used.

Chlorination (eq 1) and bromination (eq 2) were accomplished using sulfuryl chloride and *N*-bromosuccinimide with a catalytic amount of *i*-Pr_2NH as base.[12] 4-Chloro-3-hydroxy-2-pyridone **2d** and 4-bromo-3-hydroxy-2-pyridone **2e** were obtained in 75% and 78% yields, respectively. Pyridone **2a** underwent allylation of its phenolic group with ease (eq 3). Subjecting the *O*-allyl product under refluxing conditions, Claisen rearrangement provided 4-allyl-3-hydroxy-2-pyridone **2f** in good yield.[13] Catalytic hydrogenation of **2f** reduced only the terminal alkene while keeping the aromatic 2-pyridone core intact, providing 3-hydroxy-4-propyl-2-pyridone **2g**. *O*-TBS-protected **2e** and



10.1021/ja900582a CCC: $40.75

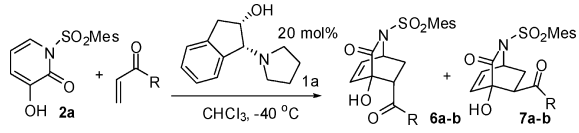
Table 2. Diels−Alder Reactions of 4-Substituted 3-Hydroxy-2-pyridones **2d**−**h**



entry	**2**[R^1]	R^2	adduct	yield/%[a]	ee/%[b]
1	**2d**[Cl]	Ph	**5a**	90	92
2	**2d**[Cl]	Et	**5b**	88	94
3	**2d**[Cl]	4-MeC_6H_4	**5c**	94	95
4	**2e**[Br]	Ph	**5d**	92	90
5	**2e**[Br]	Et	**5e**	91	90
6	**2e**[Br]	Bn	**5f**	92	90
7	**2f**[Allyl]	Ph	**5g**	89	87
8	**2f**[Allyl]	4-MeC_6H_4	**5h**[c]	90	96
9	**2g**[*n*-Propyl]	Ph	**5i**	93	83
10	**2g**[*n*-Propyl]	Et	**5j**	90	83
11	**2h**[4-ClC_6H_4]	Ph	**5k**	89	88

[a] Isolated yield. [b] Chiral HPLC. [c] Absolute configuration of **5h** determined by X-ray analysis.

Table 3. Diels−Alder Reactions between **2a** and Alkyl Vinyl Ketones



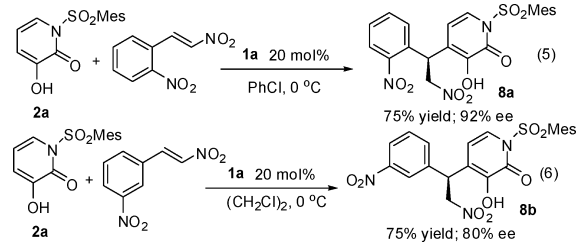
entry	R	**6**/**7**[a]	yield/%[b]	ee/%[c]
1	Me	3:1	85	91, 91
2	Et	3:1	86	90, 90

[a] Diastereomic ratio by HPLC. [b] Yield of both isomers. [c] Chiral HPLC.

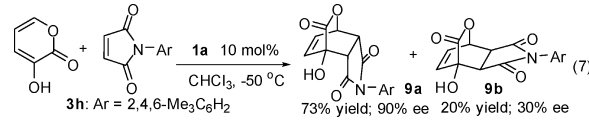
para-chlorobenzene boronic acid coupled smoothly under Suzuki conditions (eq 4).[14] The TBS group was removed with $BF_3 \cdot Et_2O$ to give **2h** in good overall yield. Chloro- (Table 2, entries 1−3) and bromo- (entries 4−6) substitutions at the C4 position did not affect the Diels−Alder reaction dramatically; high ee's were observed for several maleimides used. While the sizes of the allyl (entries 7−8) and *n*-propyl (entries 9−10) groups were similar, the allyl substituted pyridone often gave slightly better ee's. 4-Chlorophenyl-3-hydroxy-2-pyridone **2h** also gave a Diels−Alder adduct with a good level of ee (entry 11). We were not able to access C5 and C6 derivatives of 3-hydroxy-2-pyridones as selective electrophilic substitution of these positions seems to be nontrivial.

Terminal olefins such as vinyl ketones were used as dienophiles in the Diels−Alder reactions. Reactions at room temperature gave ee's around 50% and were improved to 90% with a dr of 3:1 when the reaction was carried out at −40 °C (Table 3, entries 1−2). The structures of Diels−Alder adducts **6** and **7** were elucidated using $^1H-^1H$ COSY and NOE experiments (see Supporting Information, SI). The acrylates, however, gave only the *endo* diastereoisomer with an ee of up to 70% when subjected to the same reaction conditions. These experiments illustrated the versatility of this methodology; both cyclic and acyclic dienophiles can be used.

When β-nitro styrenes were used as the dienophiles, Aldol−Michael adducts **8a**−**b** were obtained (eqs 5, 6). Adducts **8a**−**b** resulted from pyridone **2a** behaving exclusively as an alpha enol. Only one single isomer was obtained, and gamma-enol (homoenol) addition was not observed. This provided an indication that it is possible to tune the reactivity of hydroxy-pyridones to behave as a diene, an alpha-enol, or a gamma-enol. The absolute configuration of **8a** was elucidated using X-ray analysis (see SI).



When **1a** was used to catalyze the Diels−Alder reaction of 3-hydroxy-2-pyrone and *N*-mesitylmaleimide, a high level of ee was observed for the major diastereoisomer **9a** (eq 7). Unlike the reaction between 3-hydroxy-2-pyridone and vinyl ketones, the *exo* isomer **9b** gave a low level of ee.



In summary, a new bifunctional catalyst **1a**, containing both Brønsted base and hydrogen bonding donor moieties, has been identified. It is easily prepared in a single step from commercially available amino-indanol. It was found to be an excellent catalyst for Diels−Alder reactions of both 3-hydroxy-2-pyridone and 3-hydroxy-2-pyrone. Work is ongoing to utilize the Diels−Alder adducts as a starting material for natural product synthesis.

Acknowledgment. This work was supported by grants (R-143-000-337-112 and R-143-000-342-112) and a scholarship (to J.S.) from the National University of Singapore.

Supporting Information Available: Experimental procedures, characterization, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review of Diels−Alder reactions in total synthesis, see:(a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.
(2) For a review of Diels−Alder reaction, see:(a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667.
(3) For a review on the use of Brønsted acids or bases as catalysts in Diels−Alder reactions, see:(a) Shen, J.; Tan, C.-H. *Org. Biomol. Chem.* **2007**, *6*, 3229–3236.
(4) For a review of Diels−Alder reactions with 2-pyridones, see:(a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111–9171.
(5) (a) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364–6365. (b) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422–2423.
(6) Okamura, H.; Nagaike, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2000**, *41*, 8317–8321.
(7) Böhm, M.; Lorthiois, E.; Meyyappan, M.; Vasella, A. *Helv. Chim. Acta* **2003**, *86*, 3787–3817.
(8) For a review of hydrogen bond catalysts applied in enantioselective reactions, see:(a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510.
(9) For selected examples, see:(a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279–1281. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673. (c) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907. (d) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576–6579.
(10) Other sulfonyl protecting groups such as methyl sulfonyl and 2-naphthyl sulfonyl gave low conversions of the D−A adducts.
(11) (a) Komiyama, T.; Takaguchi, Y.; Tsuboi, S. *Tetrahedron Lett.* **2004**, *45*, 6299–6301. (b) Komiyama, T.; Takaguchi, Y.; Gubaidullin, A. T.; Mamedov, V. A.; Litvinov, I. A.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 2541–2547.
(12) (a) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **1995**, *36*, 3893–3896. (b) Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576–1579.
(13) Moffett, R. B. *J. Org. Chem.* **1963**, *28*, 2885–2886.
(14) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

JA900582A