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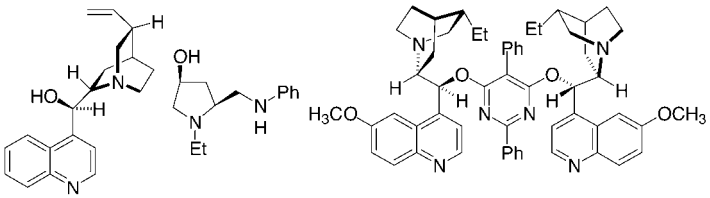
# A Highly Enantioselective and General Conjugate Addition of Thiols to Cyclic Enones with an Organic Catalyst**

Paul McDaid, Yonggang Chen, and Li Deng*

Enantioselective conjugate addition is a fundamentally important transformation in asymmetric synthesis.[1] Catalytic enantioselective conjugate addition to cyclic enones has attracted considerable attention as a general and attractive strategy for the synthesis of optically active cyclic building blocks. A number of general and highly enantioselective conjugate additions of carbon nucleophiles to cyclic enones catalyzed by transition metals have been reported recently.[2] Excellent enantioselectivity has also been obtained in the conjugate addition of carbon nucleophiles to cyclohexenone and α,β-unsaturated aldehydes with organic catalysts.[3] However, the development of a general and highly enantioselective 1,4-addition of thiols to cyclic enones remains a challenging goal despite numerous attempts involving metal-based catalysts,[4] phase-transfer catalysts,[5] and organic catalysts.[6–11] We describe here significant progress toward accomplishing this goal using a readily available chiral organic catalyst.

Pioneering studies by Wynberg et al.[6] and Mukaiyama et al.[7] on the asymmetric 1,4-addition of thiols promoted by organic catalysts pinpointed chiral cyclic amines bearing a β-hydroxy group such as cinchonidine (**1**) and the proline-derived compound **2** as promising catalysts. The highest



**1** **2** (DHQD)$_2$PYR **3**

enantioselectivities obtained with catalysts **1** and **2** in the conjugate additions of thiols to 5,5-dimethylcyclohexenone and cyclohexenone, respectively, are 75 and 88% *ee*.[6, 7] Unfortunately, in additions to other cyclic enones enantioselectivity was found to decrease significantly (<70% *ee*) with either catalyst.[6, 7] Since modification or removal of the hydroxy group of catalysts **1** and **2** led to drastically reduced catalyst efficiency, the enantioselective catalysis of **1** and **2** was attributed to a bifunctional mechanism involving the simultaneous activation of the cyclic enone and the thiol by the hydroxy and the amino groups, respectively.[6, 7] However, we recently observed that commercially available ethers of mono- and biscinchona alkaloids are more effective than natural cinchona alkaloids as chiral Lewis base catalysts for asymmetric nucleophile – electrophile reactions.[12] These observations prompted us to explore the possibility of using a modified cinchona alkaloid to catalyze highly enantioselective 1,4-additions of thiols to cyclic enones.

We first examined natural and modified cinchona alkaloids for their ability to promote enantioselective conjugate addition of thiophenol to cyclohexenone [Eq. (1)]. As illustrated in Table 1, modified cinchona alkaloids bearing no hydroxy groups are comparable to cinchonidine (**1**) in their catalytic activity. Especially notable is that the bis(dihydroquinidinyl)pyrimidine derivative (DHQD)$_2$PYR (**3**) was shown to be more effective than cinchonidine (**1**). Lacking a hydrogen donor, (DHQD)$_2$PYR (**3**) is unable to promote the enantioselective conjugate addition by means of a bifunctional catalysis mechanism similar to that proposed for **1** and **2**.[6, 7] Furthermore, reactions promoted by **3**, which was derived from quinidine, gave in excess the *R* isomer of the

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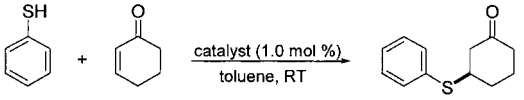
Table 1. Effect of the catalyst on the asymmetric 1,4-addition of thiophenol to cyclohexenone [Eq. (1)].




(1)

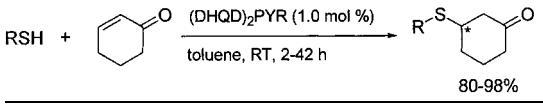
| Entry | Catalyst[a] | $t$ [h] | Yield [%][b] | $ee$ [%][c,d] |
|---|---|---|---|---|
| 1 | quinidine | 24 | 81 | 30[e] |
| 2 | cinchonidine | 14 | 90 | 44 |
| 3 | DHQD-CLB | 4 | 87 | 10 |
| 4 | DHQD-PHN | 4 | 88 | 19 |
| 5 | DHQD-MEQ | 2 | 98 | 22 |
| 6 | $(DHQD)_2PHAL$ | 16 | 91 | 18 |
| 7 | $(DHQD)_2AQN$ | 23 | 93 | 21 |
| 8 | $(DHQD)_2PYR$ (**3**) | 19 | 91 | 53 |

[a] See Supporting Information for the structures of the catalysts. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] The absolute configuration of the product was determined to be *R* (see Supporting Information). [e] The *S* enantiomer of the product was obtained as the major isomer.

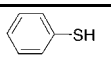
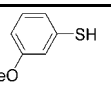
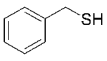
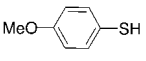
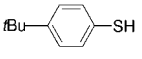
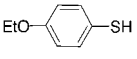
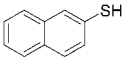
Michael adduct, while the quinidine-promoted reaction generated the *S* isomer as the major product (Table 1). The sense of asymmetric induction of the 1,4-addition of thiophenol to cyclohexenone catalyzed by the modified cinchona alkaloid, with respect to the absolute configuration of C9 and C10 of the cinchona alkaloid skeleton, is therefore opposite to that obtained with natural cinchona alkaloids. This indicates that the corresponding mechanisms for the conjugate additions catalyzed by the modified and natural cinchona alkaloids must differ significantly.

We next turned our attention to the effect of altering the structure of the thiol on the enantioselectivity of the reaction [Eq. (2)]. We found that certain 3- or 4-substituted thiophenols gave substantially improved enantioselectivities (Table 2, entries 5–7 vs entry 1). Interestingly, the $(DHQD)_2PYR$-catalyzed conjugate addition of 4-*tert*-butylthiophenol, the best Michael donor for conjugate additions catalyzed by **1**[6] and **2**,[7] gave poor enantioselectivity (entry 3). The optimal enantioselectivity at room temperature was obtained with the commercially available 2-thionaphthol (entry 8).

Table 2. Asymmetric 1,4-addition of thiols to cyclohexenone catalyzed by $(DHQD)_2PYR$ (**3**) [Eq. (2)].



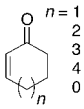
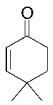

(2)

| Entry | RSH | $ee$ [%][a] | Entry | RSH | $ee$ [%][a] |
|---|---|---|---|---|---|
| 1 |  | 53 | 5 |  | 64 |
| 2 |  | 21 | 6 |  | 65 |
| 3 |  | 30 | 7 |  | 66 |
| 4 |  | 41 | 8 |  | 77[b] |

[a] Determined by HPLC analysis (see Supporting Information). [b] The absolute configuration of the major enantiomer was determined to be *R* (see Supporting Information).

We were pleased to find that excellent enantioselectivity could be attained for 2-thionaphthol when the reaction was performed at $-60\,^{\circ}C$ with 1.0 mol% catalyst (Table 3, entry 1). Most importantly, excellent enantioselectivities are achieved with a wide range of cyclic enones. Enantiomeric

Table 3. Asymmetric 1,4-addition of 2-thionaphthol to cyclic enones catalyzed by $(DHQD)_2PYR$ (**3**).

| Entry | Enone | T [°C] | $t$ [h] | Yield [%][a] | $ee$ [%][b] |
|---|---|---|---|---|---|
| 1 |  ($n$ = 1, 2, 3, 4, 0) | −60 | 17 | 77 | 94[c] |
| 2 | | −60 | 20 | 86 | 97 |
| 3 | | −60 | 30 | 82 | > 99 |
| 4 | | −60 | 48 | 91 | 97 |
| 5 | | −60 | 23 | 55 | 41 |
| 6 |  | −55 | 69 | 71 | 92 |
| 7[d] |  | −50 | 120 | 88 | 95 |
| 8 |  | −60 | 64 | 88 | 93 |

[a] Yields of isolated products. [b] Determined by HPLC analysis (see Supporting Information). [c] The absolute configuration of the product was determined to be *R* (see Supporting Information). [d] 1.6 mol% catalyst was employed in this reaction.

excesses ranging from 93% to greater than 99% are obtained for six- to nine-membered cyclic enones and various substituted cyclohexenones (Table 3). Although moderate enantioselectivity is obtained with cyclopentenone (entry 5), highly enantioselective conjugate addition is accomplished with 4,4-dimethyl cyclopentenone (entry 6). To our knowledge, there is only one example with 90% *ee*[4] among the reported catalytic asymmetric Michael additions of thiols to cyclic enones.[1, 4, 6, 7]

In conclusion, we have realized the first reported general and highly enantioselective catalytic asymmetric 1,4-addition of thiols to cyclic enones which uses an organic catalyst. Our results also extend the scope of chiral Lewis base catalysis by modified cinchona alkaloids to a new class of important reactions. Future studies in our laboratories will focus on elucidating the mechanism of catalysis and expanding the synthetic utility of the reaction.

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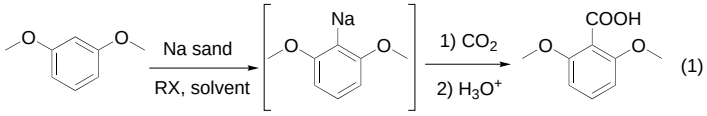
## Directed *ortho*-Metalation, a New Insight into Organosodium Chemistry**

Arnaud Gissot, Jean-Michel Becht, Jean Roger Desmurs, Virginie Pévère, Alain Wagner,* and Charles Mioskowski*

From laboratory to industrial scale, the use of strong organoalkali metal bases is almost exclusively restricted to alkyllithium derivatives.[1] They are commercially available as 1–2 M solutions, quite stable and easily generated from alkylhalides and lithium. In contrast, the synthesis of alkylsodium compounds is much more troublesome and requires high-speed mechanical stirring, low temperatures, and excess sodium.[2–6] Under classical conditions, organohalides react with sodium to give mainly Wurtz coupling products.[7, 8] Moreover, alkylsodium compounds show poor stability, especially in ethereal solvents.[9, 10] As a consequence, in spite of the low cost of metallic sodium and the sometimes demonstrated interesting reactivity,[11] alkylsodium compounds have not been considered so far as valuable organometallic reagents in organic synthesis.

Herein we report on a straightforward and efficient one-pot *ortho*-metalation procedure relying on the generation of sodiated organic bases from RCl and a stoichiometric amount of metallic sodium in the presence of aromatic substrates.[12] Under these conditions, handling and storage of alkylsodium compounds is avoided and *ortho*-metalation is favored over usual coupling and solvolysis side reactions.[13]

1,3-Dimethoxybenzene (1,3-DMB), known to undergo *ortho*-metalation with alkyllithium bases in good yields,[14] was selected as a model substrate to investigate the scope of the reaction with alkylsodium compounds [Eq. (1)]. Several parameters, including solvent, temperature, and the nature of the organohalide, were varied (Table 1). All reactions were quenched by addition of dry-ice, and the yield of acid [see Eq. (1)] was considered as indicative of the metalation efficiency.[15]



(1)

Table 1. Influence of some parameters on the directed *ortho*-sodiation of 1,3-DMB [Eq. (1)].[a]

| Entry | RX | Solvent | $T$ [°C] | Yield [%] |
|---|---|---|---|---|
| 1 | 1-chlorooctane | toluene | 20 | 70 |
| 2 | 2-chloropropane | toluene | 20 | 8[b] |
| 3 | 2-bromopropane | toluene | 0 | 21 |
| 4 | chlorobenzene | toluene | 20 | 35[c] |
| 5[d] | 1-chlorooctane | $Et_2O$ or THF | 20 | 45 or 86 |
| 6 | 1-chlorooctane | THF or toluene | −15 | 30 or 28 |
| 7 | 1-chlorooctane | toluene | 110 | 20 |

[a] The sodium sand was obtained by dispersing melted sodium under vigorous mechanical stirring; see Experimental Section. [b] $T$ = room temperature or 0 °C. [c] 2,6-dimethoxybiphenyl was also isolated in 35% yield.[16, 17] [d] $Me_2SO_4$ instead of $CO_2$ used as electrophile.

In the presence of 1-chlorooctane (or 1-chloropropane) 2,6-dimethoxybenzoic acid was obtained in 70% yield (entry 1), comparable to the yield of classical *n*BuLi metalations.[14] When the reaction was conducted in a two-step manner, that is, when the alkylsodium compound was synthesized prior to the addition of 1,3-DMB, only trace amounts (<1%) of carboxylic acid were detected. The sterically hindered neopentyl chloride did not give any metalation product, and secondary chloroalkanes gave poor results (entry 2).[3a] As expected, primary bromoalkanes were too reactive toward sodium, even at low temperature. Yet, secondary bromoalkanes, with a lower tendency to undergo Wurtz coupling, gave the desired acid in moderate yield (entry 3).

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