1F2b Asymmetric synthesis of multi-functionalized cyclopropanations with chemically modified cinchona alkaloids

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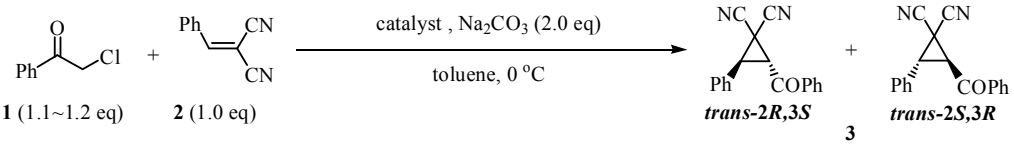
Owing to their intrinsic strained structure, cyclopropanes are often utilized as reactive synthetic intermediates. Therefore, the asymmetric synthesis of this group of compounds has gained considerable interest. We have previously reported that cinchonidine serves as an effective catalyst in the cyclopropanation reaction between α-chloroacetophenone (**1**) and phenylmethylidene-malononitrile (**2**), and that the position of the hydroxyl group influences the stereochemical outcome of the reaction (entries 1 and 4).[1] In order to improve selectivity and possibly gain insight to the mechanism of the reaction, we have prepared and examined a variety of other cinchona alkaloid derivatives. It was found that reduction of the ethenyl group of cinchona alkaloids to ethyl somehow improves the selectivity (entries 1 and 2, 4 and 5). Furthermore, the introduction of a 1-adamantyl ester group led to an increase up to -91 %ee (entry 6). Currently, we are extending our examination to other derivatives.

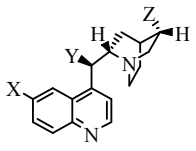
Table



1 (1.1~1.2 eq) **2** (1.0 eq) ***trans*-2*R*,3*S*** + ***trans*-2*S*,3*R*** **3**

entry	catalyst	cat.	time (d)	yield (%) [a]	ee (% ee) [b]
1	**4**	0.2 eq	4	78	56
2	**5**	0.2 eq	7	77	74
3	**6**	0.2 eq	3	84	59
4	**7**	0.2 eq	5	51 (61)	-52
5	**8**	0.2 eq	7	82 (86)	-72
6	**9**	0.2 eq	5	80 (89)	-91
7	**9**	0.01 eq	5	39 (93)	-44

[a] Conversion yields are in parentheses. [b] Determined by HPLC (chiralcel OD). Values without a sign refer to products with an excess of the trans-2*S*,3*R* enantiomer.



4: X = H, Y = OH, Z = ethenyl
5: X = H, Y = OH, Z = ethyl
6: X = OTBDPS, Y = OH, Z = ethenyl
7: X = OH, Y = OBn, Z = ethenyl
8: X = OH, Y = OBn, Z = ethyl
9: X = OH, Y = $AdOCO_2$, Z = ethyl

Ad = 1-adamantyl

(1) Kojima, S.; Suzuki, M.; Watanabe, A.; Ohkata,K. *Tetrahedron Lett.,* **2006***, 47,* 9061-9065.