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Catalytic Asymmetric Nazarov Reactions Promoted by Chiral Lewis Acid Complexes

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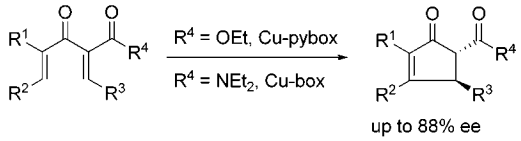
ABSTRACT



Divinyl ketones bearing α-ester or α-amide groups undergo Nazarov cyclizations to give cylopentenones using copper–bisoxazoline Lewis acid complexes with moderate to good ees.

The Nazarov cyclization is a cationic electrocyclic reaction that, although initially found to be promoted by strong protic acids, has since been shown to be promoted by milder, Lewis acids (the reaction may also be promoted photochemically).[1] Since this discovery, the scope of the reaction has been increased, most notably by Denmark's silicon-directed reaction[2] and West's "interrupted" Nazarov reaction.[3] However, asymmetric induction has not been widely explored, with only the related cyclopentannelation reaction reported by Tius,[4] which exploits the axial chirality of allenes, and three chiral auxiliary-promoted reactions[5] described thus far.

During the acid (Lewis or protic)-promoted Nazarov cyclization, a 4-π conrotatory electrocyclic reaction occurs, and therefore, asymmetric induction can be achieved if one is able to control the direction of the conrotation.

On the basis of the seminal contributions from Evans, we believed that the use of divinyl ketones bearing an α-ester group together with copper bisoxazoline complexes offered some potential to control the direction of conrotation. From X-ray analysis, Evans had found that complexes between copper bisoxazolines and related alkylidene malonates adopted a boat conformation **1** in which the copper and alkenyl groups were positioned at the apex, Figure 1.[6]

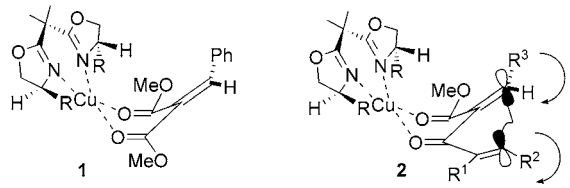


Figure 1. Boat conformation in Evans' asymmetric Michael addition of alkylidene malonates.

If the distortion of the copper-complexed alkylidene malonate also occurs with divinyl ketoesters, one could expect the alkene moiety to be pushed out of the plane of

(1) S. E. Denmark, In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 751. (b) Santelli-Rouvier, C.; and Santelli, M. *Synthesis* **1983**, 429−442. (c) Ramaiah, M. *Synthesis* **1984**, 529−571.

(2) Denmark, S. E.; Wallace, M. A.; Walker, C. B. *J. Org. Chem.* **1990**, *55*, 5543−5545 and references therein.

(3) Bowder, C. C.; Marmsäter, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033−3035 and references therein.

(4) Hu H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895−9896.

(5) (a) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrose, C.; Haltiwanger, R. C. *Synlett* **1999**, 1612−1614. (b) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* 2003, 1380−1381. (c) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447−2450. (d) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514. (e) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091−10100.

(6) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, 121, 1994−1995. (b) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142.

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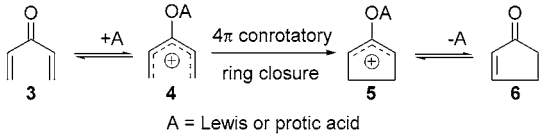


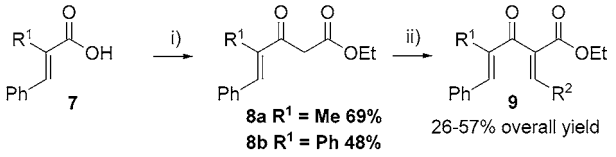
Figure 2. Nazarov cyclization pathway.

the 1,3-dicarbonyl group (complex **2**) and thereby control the direction of conrotation.

The presence of an α-ester group will, however, necessarily result in a retardation in rate because electron-withdrawing groups in the α-position destabilize intermediate **5** (Figure 2) which is formed in the RDS.[1]

The α-ester-substituted divinyl ketones were prepared in good yield by nucleophilic addition of the enolate of ethyl acetate to the acid chloride of the corresponding cinnamic acid followed by Knovenagel condensation of the resulting *β*-keto ester with the appropriate aldehyde, Table 1.[7]

Table 1. Synthesis of Divinyl Ketones[a]



entry	R^1	R^2	yield of **9** (%)[b]
1	**Me**	Ph	83
2	**Me**	Me	81
3	**Me**	*p*-NO_2Ar	67
4	**Ph**	Ph	52
5	**Ph**	Me	55

[a] Reagents and conditions: (i) (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C; (b) LDA, EtOAc, THF, −78 °C. (ii) (a) $TiCl_4$, CCl_4, THF, 0 °C; (b) R^2CHO, THF, 0 °C; (c) pyridine, 0 °C to rt. [b] Yields quoted are from **8a** and **8b**, respectively.

Initial investigations using substrate **9a** with $CuBr_2$,[8] ligand, and $AgSbF_6$ in dichloromethane showed us that the cyclization could be promoted by bisoxazoline-based Lewis acid complexes, and the results are shown in Table 2.

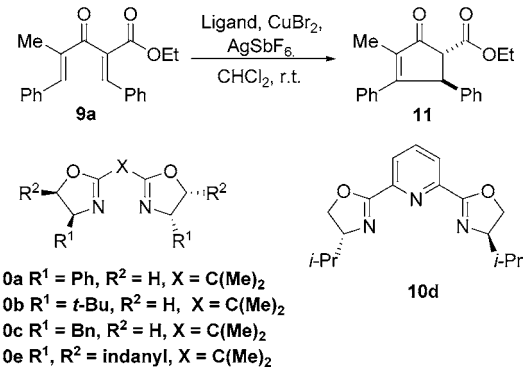
Phenyl-substituted bisoxazoline **10a** gave good yield but low enantioselectivity. Improved enantioselectivity was observed with *tert*-butyl-substituted bisoxazoline **10b** (entry 2), but switching to the pyridyl bisoxazoline **10d** (entry 4) resulted in even higher selectivity (71% ee).

The yields and enantioselectivity of the cyclizations were found to be rather capricious until the precipitated silver salts were removed by filtration. This was achieved by filtering the reaction at two stages through 0.45 μm syringe tip filters,[9]

(7) Andrews, J. F. P.; Regan, A. C. *Tetrahedron Lett.* **1991**, *32*, 7731−7734.

(8) $ZnBr_2$, $FeBr_2$, $InBr_3$, $Cu(OTf)_2$, $Sc(OTf)_2$, and $Yb(OTf)_3$ were all tested, but $CuBr_2$ proved to be the optimum metal salt.

Table 2. Initial Results of Nazarov Cyclizations[a]



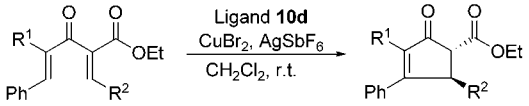
entry	ligand	yield (%)	ee (%)
1	**10a**	85	5
2	**10b**	70	44
3	**10c**	37	5
4	**10d**	35	71
5	**10e**	28	17
6[b]	**10d**	73	76

[a] All reactions were carried out with 1 equiv of ligand complex. [b] This reaction was carried out using an improved procedure of filtration of the copper/ligand complex and removal of the precipitated silver salts.

which removed any unwanted decomplexed $CuBr_2$ and silver salts. This method, which gives a homogeneous reaction mixture, resulted in improved yields and perfectly reproducible ees, Table 2, entry 6.

These results were obtained using 1 equiv of ligand complex; lower catalyst loadings resulted in a corresponding decrease in yield (Table 3, entry 2). Attempts to increase turnover using molecular sieves,[10] hexafluoro-2-propanol,[11] $NaBPh_4$,[12] $LiClO_4$,[12] and TMSCl (to trap the product) were unsuccessful.

Table 3. Nazarov Cyclizations under Improved Conditions



9a R^1 = Me, R^2 = Ph
9b R^1 = Ph, R^2 = Ph
9c R^1 = Me, R^2 = Me
9d R^1 = Ph, R^2 = Me
9e R^1 = Me, R^2 = *p*-NO_2-Ar

11a R^1 = Me, R^2 = Ph
11b R^1 = Ph, R^2 = Ph
11c R^1 = Me, R^2 = Me
11d R^1 = Ph, R^2 = Me
11e R^1 = Me, R^2 = *p*-NO_2-Ar

entry	substrate	equiv	yield (%)	ee (%)
1	**9a**	1.0	73	76
2	**9a**	0.5	42	78
3	**9b**	1.0	98	86
4	**9b**	0.5	96	86
5	**9c**	1.0	35	3
6	**9c**	0.5	27	1
7	**9d**	1.0	86	42
8	**9d**	0.5	86	35
9	**9e**	1.0	24	74
10	**9e**	0.5	17	79

The only previous examples of Nazarov cyclizations that have employed catalytic quantities of Lewis acid[3] employed nucleophiles to trap the intermediate allyl cation **5**, the most effective of which was Et_3SiH. However, even this strategy was unsuccessful,[13] furnishing low yields and reduced enantioselectivity, and so we decided to explore the scope of the optimized conditions using 1 equiv of the catalyst (Table 3).

Entries 3 and 4, Table 3, show that the inclusion of a phenyl group at R^1 results in higher selectivity and greatly improved catalytic activity. Alkyl groups at R^2 result in lower enantioselectivity (entries 7, 8), and substrates bearing small alkyl groups at R^1 and R^2 furnish essentially racemic product (entries 5, 6). These observations show that a bulky substituent at R^1 promotes turnover and enantioselectivities. High enantioselectivities are achieved with large groups at R^2. Large groups at R^1 also give higher enantioselectivity than smaller groups, but this site is less sensitive toward steric hindrance than R^2.

Divinyl ketones bearing α-amide groups were also considered as potential substrates, as they would be expected to provide similar control in the conformation of the Lewis acid−substrate complex, but their decreased electron-withdrawing ability in comparison to esters should result in faster reactions. Suprisingly, such substrates had never been tested before in Nazarov cyclizations.

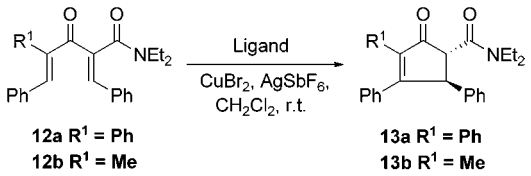
However, rather than improved rates, we observed little reactivity at all from substrate **12a** and the py-box ligand **10d** using the previously optimized conditions. We therefore explored other bisoxazolines (**10a**−**c**) and this time found that ligands **10a** and **10b** were very effective in terms of yield and enantioselectivity. Using amide substrates, high enantioselectivity was observed with both alkyl and aryl substituents at R^1 (Table 4, entries 1, 5). However, as before, turnover was limited.

Attempts to determine the absolute stereochemistry of the cyclization products of **11** and **13** by X-ray crystallography techniques of suitable derivatives were unsuccessful due to the needle morphology of the crystals. We therefore turned to the use of Mosher's ester derivatives,[14] which have been used to assign the absolute stereochemistry of secondary alcohols by ^1H NMR through the analysis of chemical shift differences between the two ester diastereomers.[15] This required alcohol **14**, which was readily prepared from **11b**.

Reduction of the ketoester **11b**[16] followed by selective MEM protection of the primary alcohol[17] gave rise to secondary alcohol **14**. The relative stereochemistry of **14** was determined by NOE studies. The alcohol was then derivatized separately with (*R*)- and (*S*)-1-methoxy-1-phenyl-1-trifluoromethylacetic acid (MTPA), respectively, to give both diastereomers of the Mosher's ester **15** and **16**.

Analysis of the ^1H NMR spectrum (run in $CDCl_3$) of the diastereomers **15** and **16** revealed that the signal for the proton α to the *O*-MTPA group (circled) appeared upfield in the (*R*)-MTPA diastereomer compared with the (*S*)-MTPA diastereomer, indicating a shielding interaction with the phenyl group of the MTPA in the (*R*)-enantiomer. The absolute stereochemistry of the cyclized product must therefore have an all-(*R*)-configuration as drawn in Scheme 1. To determine the absolute stereochemistry of the keto amide substrates **13**, the keto ester **11b** of known absolute configuration was converted into the corresponding amide (Scheme 2).[18] Comparison of the HPLC trace of this amide with **13a**

Table 4. Nazarov Cyclization of Amide Bearing Substrates

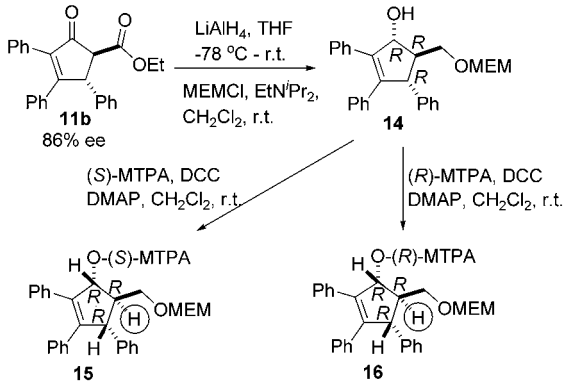


12a R^1 = Ph, **12b** R^1 = Me — **13a** R^1 = Ph, **13b** R^1 = Me

entry	substrate	L[a]	equiv	yield (%)	ee (%)
1	**12a**	**10a**	1.0	80	88
2	**12a**	**10a**	0.5	56	86
3	**12a**	**10b**	1.0	92	86
4	**12a**	**10b**	0.5	56	87
5	**12b**	**10b**	1.0	72	84
6	**12b**	**10b**	0.5	56	85
7	**12b**	**10a**	1.0	21	75
8	**12b**	**10c**	1.0	29	44

[a] L = ligand.

Scheme 1. Synthesis of the Moshers' Esters



(9) (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815. (b) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

(10) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649.

(11) See ref 6 and: Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568−570.

(12) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884−1888.

(13) Gray/brown solid was seen to form on the inside of the flask during the course on the reaction when Et_3SiH was used.

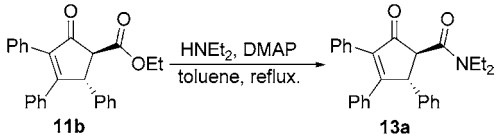
(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

(15) (a) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915−2925. (b) Kuoda, K.; Ooi, T.; Kusumi, T. *Tetrahedron Lett.* **1999**, *40*, 3005−3008.

(16) Brewster, A. G.; Caulkett, P. W. R.; Jessup, R. *J. Med. Chem.* **1987**, *30*, 67−70.

(17) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411−1415.

Scheme 2. Conversion of **11b** to **13a**



confirmed that they were identical, showing that both the ester **11b** and amide **13a** had the same absolute configuration.

The absolute stereochemistries of the ester- and amide-substituted divinyl ketones are consistent with a stereochemical model where the chiral bulk of the ligands distort the plane of the cationic divinyl ketone intermediate (**4**, Figure 2) to force one mode of conrotation to be favorable. Thus, in the case of the divinyl keto amide reaction catalyzed by the copper bis-oxazoline, buttressing of the *tert*-butyl group with the alkene moiety will push it away and underneath the other vinyl group therefore favoring clockwise conrotation (Figure 3).

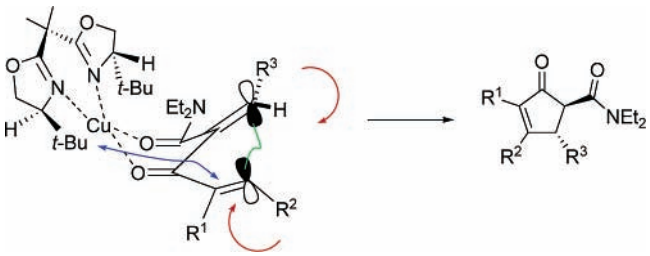


Figure 3. Stereochemical model for the interaction of bisoxazoline complexes with divinyl keto-amides.

In the same way, reaction of the divinyl keto esters with the copper py-box catalysts (which adopt a square-based pyramid geometry)[19] will result in a distorted complex in which the alkene substituents are pushed away from the *i*-Pr groups of the ligand. This then places the bonding lobes of the two corresponding orbitals in close proximity, making them predisposed to cyclization in a clockwise manner (Figure 4).

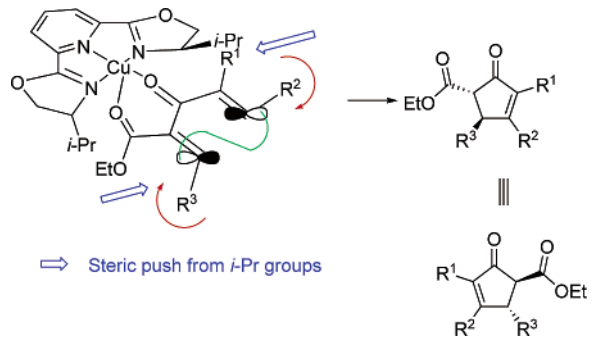


Figure 4. Stereochemical model for the interaction of py-box complexes with divinyl keto-esters.

In conclusion, we have developed the first asymmetric Nazarov cyclization promoted by chiral Lewis acid complexes, achieving good levels of enantioselectivity. Both divinyl keto esters and keto amides can be employed, with the latter showng higher levels of enantioselectivity.

Acknowledgment. We thank the EPSRC and Quest International for a CASE award (A.J.B.).

Supporting Information Available: Experimental procedures and spectral data for compounds **9a**−**e**, **11a**−**e**, **12a**,**b**, **13a**,**b**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Hoffman, R. V.; Huizenga, D. J. *J. Org. Chem.* **1991**, *56*, 6435−6439.

(19) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686−699.