RSC Advances

PAPER

Cite this: *RSC Adv.*, 2018, **8**, 41355

Enantioselective Nozaki–Hiyama–Kishi allylation-lactonization for the syntheses of 3-substituted phthalides†

Sharad V. Kumbhar[a] and Chinpiao Chen*[ab]

Received 21st November 2018
Accepted 23rd November 2018

DOI: 10.1039/c8ra09575b

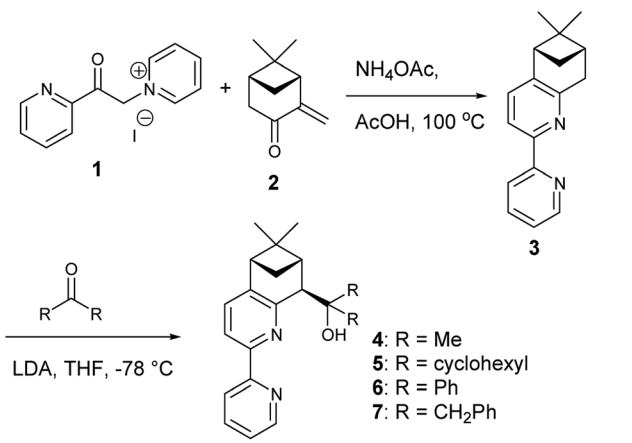
rsc.li/rsc-advances

We report the synthesis of bipyridyl ligands and these ligands were applied in the chromium-catalyzed enantioselective Nozaki–Hiyama–Kishi allylation of substituted (2-ethoxycarbonyl)benzaldehydes and subsequently lactonized to synthesize phthalides with an optimal enantioselectivity of 99%. This approach was applied to synthesize (*S*)-cytosporone E at a 71% yield in three steps.

The addition of organochromium reagents to carbonyl compounds was pioneered by Nozaki *et al.*[1] and is a versatile reaction forming carbon–carbon bonds for use with various building blocks to synthesize complex natural products and pharmaceuticals.[2] Organochromium reagents are formed *in situ* through the oxidative addition of Cr(II) species to allyl, propargyl halides, and triflates (aryl, vinyl halides, and triflates requiring catalytic amounts of Ni(II) salt)[3a,b] and can be added to aldehydes and ketones to produce the corresponding alcohols.[3] The major disadvantage of the original NHK allylation method is the excessive amount of Cr(II) salts necessary for the formation of the organochromium reagent.[1,4] Fürstner and Shi[5] reported NHK allylation that requires only catalytic amounts of active Cr(II) species; Mn is used as the reducing agent, and trimethylchlorosilane prolongs the catalytic cycle. These improvements have driven chemists to improve the enantioselectivity of this reaction. Several chiral ligands have been used as enantioselective catalysts for the allylation of aldehydes.[6] A chiral bipyridyldiol was used as the efficient enantioselective catalyst in an asymmetric NHK reaction to provide the corresponding homoallylic alcohol and simultaneously form lactone in high enantiomeric excess (90% ee).[6n] The successful application of these ligand systems motivated us to investigate the NHK allylation of (2-ethoxycarbonyl)benzaldehydes and simultaneous lactonization to produce phthalides. This approach was then employed to enantioselectively synthesize (*S*)-cytosporone E.

Pineno-bipyridyl alcohols are readily obtainable from (+)-α-pinene in four steps (Scheme 1); these steps include the stereoselective alkylation of chiral bipyridine with ketones to obtain desired products **4**–**7**.[6o] In a previous work, we used benzaldehyde, allyl chloride, and ligand **6** under Fürstner's reaction conditions to obtain the corresponding product with 70% yield and 75% ee.[6n] In the same study, a bipyridyldiol was applied under Fürstner's reaction conditions to prepare phthalide **8** with 92% yield and 90% ee. To improve the enantioselectivity of the NHK reaction using ligand **6** under Fürstner's reaction conditions, we obtained the optimal reaction conditions using benzaldehyde, allyl bromide, $CrCl_3$ (10 mol%), ligand **6** (30 mol%), and Et_3N (60 mol%) to provide a product with 83% yield and 90% ee.[6o]

Initial evaluation of non-symmetrical bipyridine ligands (**4**–**7**) in the Cr(II)-catalyzed addition of allyl bromide to (2-ethoxycarbonyl)-3,5-dimethoxybenzaldehyde revealed that ligand **6** has excellent reactivity and enantioselectivity (Table 1, entry 7). The resulting homoallylic alcohols can lactonize to give the phthalide **8**. Allylation of (2-ethoxycarbonyl)-3,5-dimethoxybenzaldehyde using Cr–**6** complex was optimized by performing the reaction in various solvents and at various reaction temperatures. (See ESI.†) Reactions performed at 0 °C



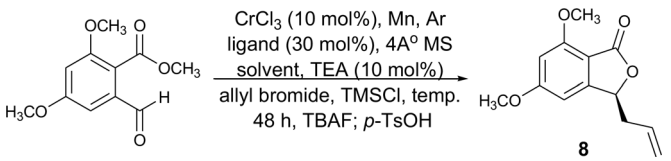
Scheme 1 Ligand synthesis.[6o]

[a]*Department of Chemistry, National Dong Hwa University, Shoufeng, Hualien 974, Taiwan. E-mail: chinpiao@gms.ndhu.edu.tw; Fax: +886 3 863 0475; Tel: +886 3 863 3597*

[b]*Department of Nursing, Tzu Chi University of Science and Technology, Hualien 970, Taiwan*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra09575b

Table 1 Optimization of chiral bipyridyl alcohol ligands for the chromium-catalyzed addition of allyl bromide to (2-ethoxycarbonyl)-3,5-dimethoxybenzaldehyde



Entry	Ligand	Solvent	Temp [°C]	Yield[a] [%]	ee[b] [%]
1	**4**	THF	r.t.	86	83
2	**5**	THF	r.t.	89	89
3	**6**	THF	r.t.	89	93
4	**7**	THF	r.t.	85	90
5	**4**	THF	0	88	87
6	**5**	THF	0	89	89
7	**6**	THF	0	86	97
8	**7**	THF	0	87	92
9	**6**	CH_2Cl_2	r.t.	58	86
10	**6**	DMF	r.t.	36	84
11	**6**	Toluene	r.t.	NR	—
12	**6**	Ether	r.t.	NR	—
13	**6**	CH_2Cl_2	0	68	89
14	**6**	DMF	0	15	82
15	**6**	Toluene	0	NR	—
16	**6**	Ether	0	NR	—

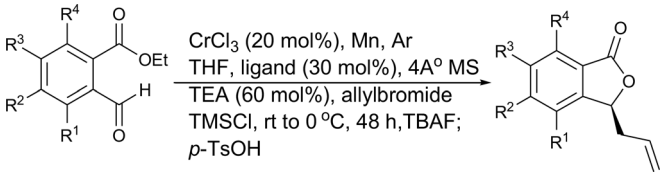
[a] Isolated yield. [b] The ee% were determined on a Chiracel OJ HPLC column.

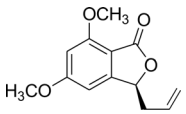
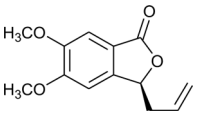
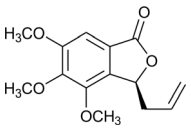
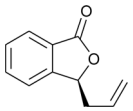
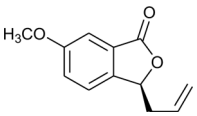
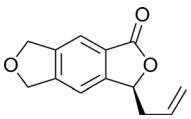
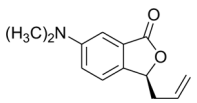
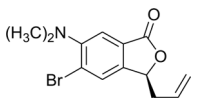
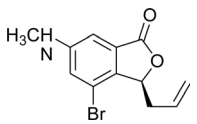
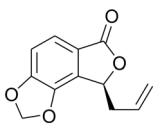
in THF afforded better results than all of screened conditions (Table 1).

Ligands **4** and **5**, which had less steric hindrance, showed slightly lower enantioselectivity than ligands **6** and **7**. The reaction conducted at room temperature resulted in a product with less enantioselectivity than the reaction at 0 °C. Table 1 shows the results of allylation using various solvents. Using toluene and diethyl ether did not result in formation of the product. Dichloromethane and DMF exhibited some transformation with low yield. THF exhibited the most desirable result, with high yield and enantioselectivity. Considering the optimized reaction conditions, we investigated the generality of the NHK allylation followed by transesterification to produce the corresponding phthalides by using various aldehydes (Table 2). All reactions were completed within 48 h and produced adducts with good to excellent yields (70%–90%) and enantioselectivities (94%–99% ee). The position and electronic properties of substituents on the aromatic ring exerted a weak influence on the enantioselectivity of the reaction. Substrates with electron-withdrawing (Table 2, entries 8 and 9), electron-donating (Table 2, entries 1–3, 5–7, and 10), and neutral (Table 2, entry 4) groups in various substitution patterns participated in this reaction efficiently (general procedure for preparation of phthalides can be found in the ESI†).

This highly enantioselective catalyst was explored to determine its promise as an enantioselective catalyst of NHK allylation–lactonization. A natural product, (*R*)-cytosporone E, was synthesized through asymmetric allylation–lactonization.

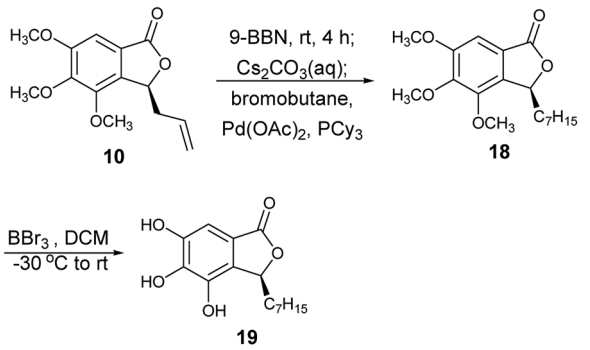
Table 2 Catalytic enantioselective synthesis of phthalides



Entry	Product		Yield[a] [%]	ee[b] [%]
1		**8**	87	97
2		**9**	85	94
3		**10**	89	99
4		**11**	86	96
5		**12**	90	97
6		**13**	76	96
7		**14**	70	96
8		**15**	90	98
9		**16**	79	97
10		**17**	77	98

[a] Isolated yields. [b] ee% were determined on a Chiracel OJ HPLC column after recrystallization.

Ohzeki and Mori synthesized (*S*)-cytosporone E with 11.5% yield (nine steps) and 45% ee using AD-mix-β® as an asymmetric dihydroxylation reagent.[7] The enantiomers of a tris(*tert*-butyldimethylsilyl)-protected derivative was separated by preparative HPLC on Chiralcel® OD to obtain pure (*S*)-



Scheme 2 Synthesis of (*S*)-cytosporone E.

cytosporone E (98.4% ee). Wyatt *et al.* synthesized racemic cytosporone E at 41.4% yield (seven steps).[8] Therefore, asymmetric NHK allylation–lactonization was used in this study as an efficient allylation reaction using ligand **6** as the enantioselective catalyst to provide the corresponding homoallylic alcohol and simultaneously form lactone **10** in a high yield (89%) and enantiomeric excess (98.8%). Lactone **10** was converted into compound **18** through treatment with 9-BBN, Cs_2CO_3(aq), bromobutane, $Pd(OAc)_2$, and PCy_3 (Scheme 2). Finally, the methoxyl groups of **18** were cleaved using BBr_3 to obtain (*S*)-cytosporone E (**19**) at 71% yield (three steps).

In summary, a chiral Cr(II) complex prepared using bipyridine alcohol and $CrCl_3$ efficiently catalyzed the enantioselective NHK allylation–lactonization of substituted (2-ethoxycarbonyl)-benzaldehyde to produce phthalides with excellent enantioselectivity (up to 99% ee). This approach was used to synthesize (*S*)-cytosporone E and obtained excellent yield and enantioselectivity.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Ms. L. M. Hsu, at the Instruments Center, National Chung Hsing University, for her help in obtaining mass spectral data, and the Ministry of Science and Technology, Taiwan, for financially supporting this research under the contract: MOST 103-2113-M-277-001-MY3.

Notes and references

1 (*a*) Y. Okude, S. Hirano, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 3179; (*b*) Y. Okude, T. Hiyama and H. Nozaki, *Tetrahedron Lett.*, 1977, **18**, 3829.

2 For reviews, see: (*a*) M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez and J. C. Palacios, *Chem. Soc. Rev.*, 1999, **28**, 169; (*b*) K. Takai and H. Nozaki, *Proc. Jpn. Acad., Ser. B*, 2000, **76**, 123; (*c*) G. C. Hargaden and P. J. Guiry, *Adv. Synth. Catal.*, 2007, **349**, 2407; (*d*) E. T. da Penha, J. A. Forni, A. F. P. Biajoli and C. R. D. Correia, *Tetrahedron Lett.*, 2011, **52**, 6342; (*e*) H.-Y. Wang, A. Kato, K. Kinami, Y.-X. Li, G. W. J. Fleetd and C.-Y. Yu, *Org. Biomol. Chem.*, 2016, **14**, 4885; (*f*) A. Gil, F. Albericio and M. Álvarez, *Chem. Rev.*, 2017, **117**, 8420; (*g*) B. Mi and R. E. Maleczka, *Org. Lett.*, 2001, **3**, 1491; (*h*) D. K. Mohapatra, P. P. Das, M. R. Pattanayak, G. Gayatri, G. N. Sastry and J. S. Yadav, *Eur. J. Org. Chem.*, 2010, 4775; (*i*) B. Wang, Y. Xie, Q. Yang, G. Zhang and Z. Gu, *Org. Lett.*, 2016, **18**, 5388.

3 (*a*) H. Jin, J.-I. Uenishi, W. J. Christ and Y. Kishi, *J. Am. Chem. Soc.*, 1986, **108**, 5644; (*b*) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto and H. Nozaki, *J. Am. Chem. Soc.*, 1986, **108**, 6048; For reviews see; (*c*) A. Fürstner, *Chem. Rev.*, 1999, **99**, 991; (*d*) L. A. Wessjohann and G. Scheid, *Synthesis*, 1999, 1; (*e*) A. S. K. Hashmi, *J. Prakt. Chem.*, 1996, **338**, 491; (*f*) A. Fürstner, *Chem.–Eur. J.*, 1998, **4**, 567.

4 (*a*) T. Hiyama, Y. Okude, K. Kimura and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 561; (*b*) T. Hiyama, K. Kimura and H. Nozaki, *Tetrahedron Lett.*, 1981, **22**, 1037; (*c*) K. Takai, K. Kimura, T. Hiyama and H. Nozaki, *Tetrahedron Lett.*, 1983, **24**, 5281.

5 (*a*) A. Fürstner and N. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 2533; (*b*) A. Fürstner and N. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 12349.

6 (*a*) M. Bandini, P. G. Cozzi, P. Melchiorre and A. Umani-Ronchi, *Angew. Chem*, 1999, **111**, 3558; *Angew. Chem. Int. Ed.*, 1999, **38**, 3357; (*b*) H. Choi, K. Nakajima, D. Demeke, F. Kang, H. Jun, Z. Wan and Y. Kishi, *Org. Lett.*, 2002, **4**, 4435; (*c*) A. Berkessel, D. Menche, C. A. Sklorz, M. Schroder and I. Paterson, *Angew. Chem*, 2003, **115**, 1062; *Angew. Chem. Int. Ed*, 2003, **42**, 1032; (*d*) M. Inoue, T. Suzuki and M. Nakada, *J. Am. Chem. Soc.*, 2003, **125**, 1140; (*e*) K. Namba and Y. Kishi, *Org. Lett.*, 2004, **6**, 5031; (*f*) M. Kurosu, M. Lin and Y. Kishi, *J. Am. Chem. Soc.*, 2004, **126**, 12248; (*g*) H. S. Schrekker, K. Micskei, C. Hajdu, T. Patonay, M. W. G. de Bolster and L. A. Wessjohann, *Adv. Synth. Catal.*, 2004, **346**, 731; (*h*) J. Lee, J. J. Miller, S. S. Hamilton and S. S. Sigman, *Org. Lett.*, 2005, **7**, 1837; (*i*) G. Xia and H. Yamamoto, *J. Am. Chem. Soc.*, 2006, **128**, 2554; (*j*) H. A. McManus, P. G. Cozzi and P. J. Guiry, *Adv. Synth. Catal.*, 2006, **348**, 551; (*k*) J. Miller and M. S. Sigman, *J. Am. Chem. Soc.*, 2007, **129**, 2752; (*l*) G. C. Hargaden and P. I. Guiry, *Adv. Synth. Catal.*, 2007, **349**, 2407; (*m*) G. C. Hargaden, T. P. O'Sullivan and P. J. Guiry, *Org. Biomol. Chem.*, 2008, **6**, 562; (*n*) X.-R. Huang, X.-H. Pan, G.-H. Lee and C. Chen, *Adv. Synth. Catal.*, 2011, **353**, 1949; (*o*) R.-Y. Chen, A. P. Dhondge, G. H. Lee and C. Chen, *Adv. Synth. Catal.*, 2015, **357**, 961.

7 T. Ohzeki and K. Mori, *Biosci., Biotechnol., Biochem.*, 2003, **67**, 2584.

8 J. D. Hall, N. W. Duncan-Gould, N. A. Siddiqi, J. N. Kelly, L. A. Hoeferlin, S. J. Morrison and J. K. Wyatt, *Bioorg. Med. Chem.*, 2005, **13**, 1409.