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Organocatalytic and Stereoselective [3 + 2] Cycloadditions of Azomethine Imines with α,β-Unsaturated Aldehydes

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Abstract: Bipyrazolidin-3-one derivatives are biologically significant compounds and their importance has increased in the past decades. In this paper, the first stereoselective [3 + 2] dipolar cycloadditions of azomethine imines with α,β-unsaturated aldehydes catalyzed by readily available α,α-diarylprolinol salts are reported, providing a facile route to the synthesis of various chiral bipyrazolidin-3-one derivatives under mild conditions. The organocatalyst **1g** with strongly electron-withdrawing groups exhibited the best stereoselectivity (*exo:endo* up to 98:2, for *exo* product up to 97% *ee*), in the combination with trifluoroacetic acid.

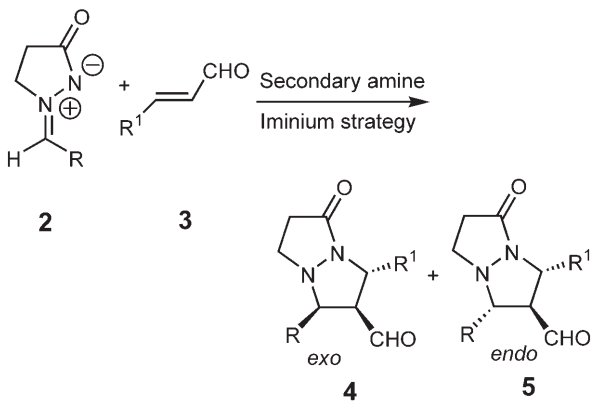
Keywords: azomethine imines; bipyrazolidin-3-one; diarylprolinols; dipolar cycloaddition; organocatalysis; unsaturated aldehydes

Recently, small organic molecules-catalyzed enantioselective transformations have attracted increasing attention.[1] Particularly, asymmetric amine catalysis has been the subject of intensive research since the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction. Numerous 1,2- or 1,4-addition reactions with excellent enantioselectivities have been reported in the last five years.[2] On the other hand, asymmetric cycloaddition reactions have also been actively explored in the amine catalysis. The generation of active iminium ions, which are thought to lower the energy of the dienophile LUMO, generally plays a key role in the successful cycloaddition reactions. Nevertheless, the current examples are mostly limited to the common Diels–Alder reactions.[3]

The catalytic asymmetric [3 + 2] dipolar cycloaddition reaction provides one of the most powerful strategies for the enantioselective construction of five-membered heterocycles. While considerable progress has been made in the metal-catalyzed asymmetric synthesis over the past decades,[4] the application of chiral organocatalysts in [3 + 2] cycloaddition reactions remains in its infancy since MacMillan's pioneering works in 2000.[5] Furthermore, only nitrones have been tested as the successful dipoles to date.[6] Based on our successful experience on the asymmetric vinylogous Michael addition of α,α-dicyanoolefins to α,β-unsaturated aldehydes catalyzed by chiral α,α-diarylprolinol salts,[7] here we present the first asymmetric [3 + 2] cycloaddition reaction of azomethine imines with α,β-unsaturated aldehydes.

Azomethine imines such as **2**, prepared by the condensation of pyrazolidin-3-one with aldehydes, are stable and easily handled compounds. Their potential application as dipoles in cycloadditions with alkenes or alkynes has been established a long time ago.[8] Several pyrazolidin-3-one derivatives exhibit biological activities, and the importance of this type of compounds has risen significantly in the last two decades. One of the examples is the cycloaddition product LY 186826, which exhibits high anti-bacterial activity.[9] On the other hand, although a variety of asymmetric cycloadditions of chiral azomethine imines have been reported,[10] the catalytic enantioselective [3 + 2] cycloadditions of pyrazolidin-3-one-derived azomethine imines are rather rare. Very recently Fu et al. have reported the highly enantioselective cycloadditions of azomethine imines with terminal alkynes catalyzed by chiral copper complexes.[11] To the best of our knowledge, the asymmetric cycloadditions of azomethine imines with α,β-unsaturated aldehydes have never been studied. We envision that the enal-activating

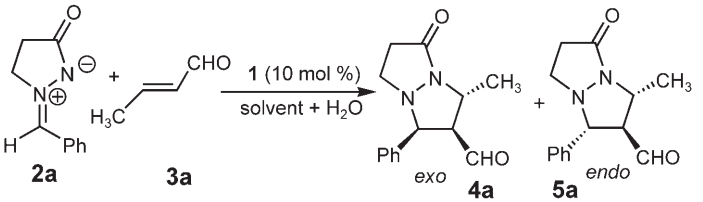
platform through iminium strategy may be suitable for these reactions (Scheme 1).



Scheme 1. [3 + 2] Cycloadditions of azomethine imines with α,β-unsaturated aldehydes.

In an initial investigation, we tested the reaction of azomethine imine **2a**[12] with crotonaldehyde **3a** in the presence of 10 mol% L-proline **1a** at room temperature (20 °C), in a mixture of nitromethane and H_2O (1 mL/6 μL)[5] (Table 1, entry 1). Gratifyingly, the desired cycloaddition product was isolated after 12 h in almost quantitative yield (*exo:endo* = 88:12), while the *ee* was only 27% (for *exo* product).[13] Inspired by these results, variously structured chiral secondary amine catalysts (Figure 1) were screened at room temperature. MacMillan's catalyst **1b** exhibited better enantioselectivity (68% *ee*) but poor diastereoselectivity (*exo:endo* = 58:42) (entry 2). Although no catalytic activity was noted in the dipolar cycloadditions of nitrones with α,β-unsaturated aldehydes by using α,α-diphenylprolinol **1c**,[6] in contrast, high catalytic activity with good stereoselectivity (*exo:endo* 77:23, 70% *ee* for *exo* product) was observed in this reaction catalyzed by **1c** and PNBA (*p*-nitrobenzoic acid) (entry 3). The *ee* was even decreased in the presence of the OH-methylated catalyst **1d** (entry 4).[14] Slightly lower *ee* was also obtained in the case of the prolinol **1e**[15] with electron-donating substituents (entry 5). A slightly better enantioselectivity was achieved when α,α-diarylprolinol **1f** was applied (entry 6). Subsequently, we were pleased to find that high enantioselectivity (85% *ee*) was obtained by employing α,α-bis-[3,5-di(trifluoromethyl)phenyl]prolinol **1g**,[16] which has strongly electron-withdrawing substituents (entry 7). In addition, the reaction conditions with regard to solvents, acidic additives and the amount of water were further optimized. The *ee* was significantly lower when $HClO_4$ (entry 8) or benzoic acid (entry 9) was applied. Although a slightly decreased *ee* was obtained by adding CF_3COOH in CH_3NO_2/H_2O (entry 10), excellent enantioselectivity (96% *ee*) was obtained in the combination of **1g** and CF_3COOH in THF/H_2O, and the reaction time could be greatly shortened (entry 11). Similar results were obtained

Table 1. Screening organocatalysts for the [3+ 2] cycloaddition of azomethine imine **2a** with crotonaldehyde **3a**.[a]



Entry	Cat. **1**	Additive	Solvent	*t* [h]	Yield[b] [%]	*exo:endo*[c]	*ee* [%][d]
1	**1a**	-	CH_3NO_2	12	99	88:12	27
2	**1b**	-	CH_3NO_2	12	99	58:42	68
3	**1c**	PNBA	CH_3NO_2	24	99	77:23	70
4	**1d**	PNBA	CH_3NO_2	24	89	78:22	63
5	**1e**	PNBA	CH_3NO_2	20	98	70:30	62
6	**1f**	PNBA	CH_3NO_2	20	94	75:25	72
7	**1g**	PNBA	CH_3NO_2	20	99	77:23	85
8	**1g**	$HClO_4$	CH_3NO_2	16	57	80:20	60
9	**1g**	PhCOOH	CH_3NO_2	40	57	79:21	69
10	**1g**	CF_3COOH	CH_3NO_2	16	81	83:17	81
11	**1g**	**CF_3COOH**	**THF**	**5**	**85**	**84:16**	**96**
12[e]	**1g**	CF_3COOH	THF	5	77	85:15	94
13[f]	**1g**	CF_3COOH	THF	6	81	84:16	96
14[g]	**1g**	CF_3COOH	THF	9	69	84:16	92
15[h]	**1g**	CF_3COOH	THF	12	89	84:16	97
16	**1g**	CF_3SO_3OH	THF	16	49	79:21	71

[a] Unless indicated otherwise, the reactions were conducted with 0.1 mmol **2a**, **2a**/**3a**/**1**/additive = 1:2:0.1:0.1, in 1 mL solvent adding 6 μL H_2O at 20 °C.
[b] Isolated yield of the mixture of *exo* and *endo* isomers.
[c] Determined by HPLC analysis.
[d] For *exo* product, determined by chiral HPLC analysis after conversion to the alcohol.
[e] 12 μL H_2O were added.
[f] 3 μL H_2O were added.
[g] No water was added.
[h] At 0 °C.

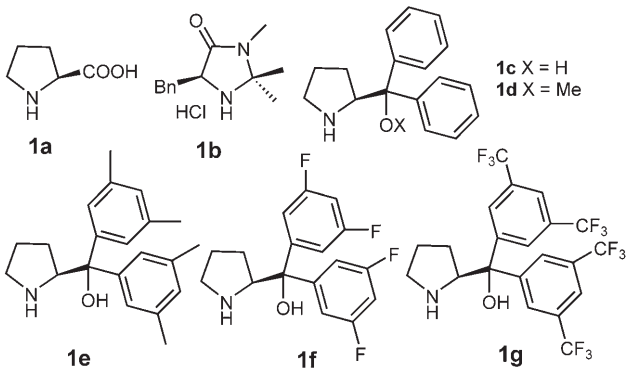


Figure 1. Structures of chiral secondary amine catalysts.

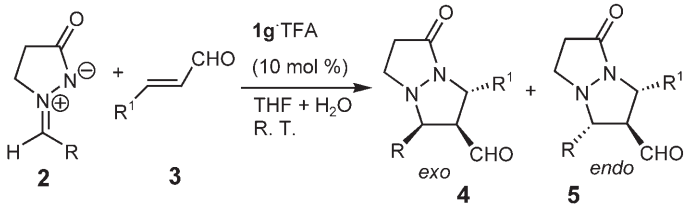
when 12 μL or 3 μL of H_2O were added (entries 12 and 13). However, the reaction rate was considerably decreased in the absence of water (entry 14). Therefore the addition of water might be helpful for the hydrolysis of the iminium intermediate after the cycloaddition reaction.[3,5] Unfortunately, the *exo*/*endo* ratio could not be further improved when the reaction was conducted at lower temperature, and similar results were observed (entry 15). In addition, a poorer *ee* was gained in the presence of more acidic CF_3SO_3H (entry 16).

With the optimal reaction conditions in hand, the scope and limitations of the organocatalytic asymmetric [3 + 2] cycloadditions of various azomethine imines with α,β-unsaturated aldehydes were explored. The results are summarized in Table 2. Excellent enantioselectivities were obtained in the reactions of azomethine imine **2a** with other linear or branched α,β-unsaturated aldehydes (Table 2, entries 1–4), and high diastereoselectivity was observed when more bulky substrate was applied (entry 4). The cycloaddition reactions also tolerated electron-withdrawing or donating substituents on the *para*-position of aryl rings of azomethine imines **2b–d**, and high enantioselectivities were generally achieved (entries 5–9). A good *ee* was still received when *ortho*-substituted substrate **2e** was employed (entry 10). Furthermore, the azomethine imine **2f** derived from an aliphatic aldehyde could be successfully reacted with crotonaldehyde, and in this case better results were obtained in the presence of MacMillan's catalyst **1b** (entry 11). Unfortunately, the cycloaddition reactions of azomethine imine **2a** or **2f** with cinnamaldehyde failed in this catalytic system, and no desired products were isolated in both reactions (entries 12 and 13). In contrast, the decomposition of the previous azomethine imine and subsequent formation of the new one of cinnamaldehyde was detected in the reaction.[17]

To determine the absolute configuration of the product of the α,α-diarylprolinol-catalyzed asymmetric 1,3-dipolar cycloaddition, compound **4f** which bears a chlorine atom was reduced to the alcohol **6** by $NaBH_4$. An X-ray analysis of crystals of **6** revealed a (*C7S, C8R, C9R*) configuration and therefore also for **4f** (Figure 2).

Based on the absolute configuration of **4f**, possible models for the intermediates in the dipolar cycloaddition reaction were proposed. As depicted in Figure 3,

Table 2. Organocatalytic [3+ 2] cycloadditions of azomethine imine **2** with α,β-unsaturated aldehydes **3**.[a]



2 3 4 5

Entry	R	R^1	*t* [h]	Prod. **4**	Yield[b] [%]	*exo*:*endo*[c]	*ee* [%][d]
1	Ph (**2a**)	Me	5	**4a**	85	81:19	96
2	Ph (**2a**)	*n*-Pr	16	**4b**	95	95:5	95
3	Ph (**2a**)	*n*-Bu	15	**4c**	85	85:15	94
4	Ph (**2a**)	*i*-Pr	20	**4d**	50	98:2	91
5	*p*-Cl-C_6H_4 (**2b**)	Me	12	**4e**	80	81:19	96
6	*p*-Cl-C_6H_4 (**2b**)	*n*-Bu	18	**4f**[e]	77	83:17	95
7	*p*-F-C_6H_4 (**2c**)	*n*-Pr	16	**4g**	77	90:10	94
8	*p*-MeO-C_6H_4 (**2d**)	*n*-Bu	18	**4h**	66	88:12	92
9	*p*-MeO-C_6H_4 (**2d**)	*i*-Pr	24	**4i**	63	98:2	83
10	*o*-Cl-C_6H_4 (**2e**)	*n*-Bu	12	**4j**	71	92:8	82
11[f]	*n*-Pr (**2f**)	Me	12	**4k**[g]	40	95:5 [h]	77
12	Ph (**2a**)	Ph	24	/	/	/	/
13	*n*-Pr (**2f**)	Ph	24	/	/	/	/

[a] The reactions were conducted with 0.1 mmol **2**, **2**/**3**/**1g**/CF_3COOH = 1:2:0.1:0.1, in 1 mL THF adding 6 μL H_2O at 20 °C.
[b] Isolated yield of the mixture of *exo* and *endo* isomers.
[c] Determined by ^1H NMR analysis.
[d] For *exo* product, determined by chiral HPLC analysis after reduction to the alcohol.
[e] The absolute configuration of **4f** was determined by X-ray analysis of the corresponding alcohol **6**. Other cycloaddition products were assigned accordingly.
[f] Catalyst **1b** was used.
[g] The corresponding alcohol was isolated.
[h] Determined by HPLC analysis of the corresponding alcohol.

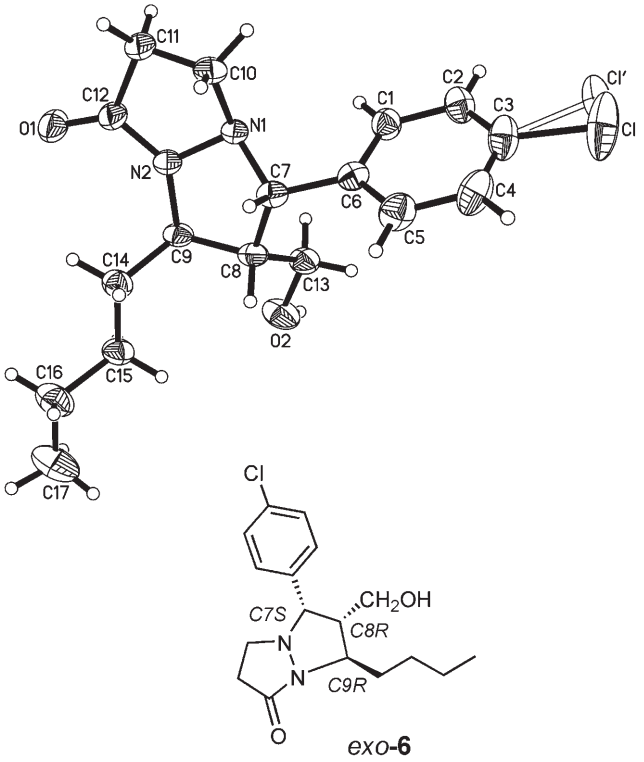


Figure 2. X-ray crystallographic structure of enantiopure **6**.

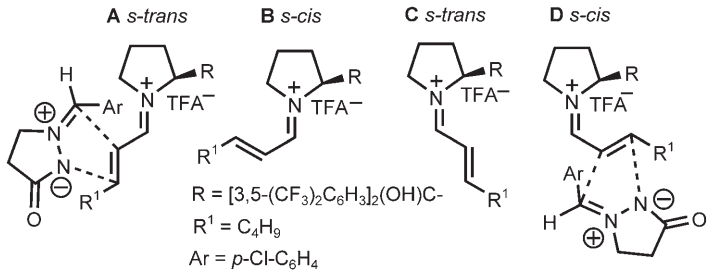


Figure 3. Possible reaction models in [3 + 2] cycloaddition of azomethine imine and unsaturated aldehyde catalyzed by **1g**.

both (*E*)- or (*Z*)-iminium isomers between α,β-unsaturated aldehyde and **1g** could be formed, and the double bond from the aldehyde can adopt either an *s-trans* or an *s-cis* conformation. Owing to the bulky α-substituents of **1g**, upside approach of the azomethine imine would be disfavored. **B** and **C** might not be the reactive intermediates because the cycloaddition must occur from the α-*si*, β-*re*-face of the dipolarophile in order to give the observed enantiomer. On the other hand, both **A** and **D** could generate the desired *exo*-adduct from the underside approach. The similar stereoselectivities have also been reported in [3 + 2] cycloaddition of α,β-unsaturated aldehydes and nitrones, and iminium isomer like **D** is thought to be the major reactive intermediate.[6b] Nevertheless, the real mechanism in current reactions still remains to be investigated.

In conclusion, we have presented the first stereoselective [3 + 2] dipolar cycloadditions of azomethine imines with α,β-unsaturated aldehydes catalyzed by readily available α,α-diarylprolinol salts. The organocatalyst **1g** with strongly electron-withdrawing groups exhibited high stereoselectivity and catalytic activity in the cycloaddtion reactions. Variously structured enantiomerical bipyrazolidin-3-one derivatives with multiple contiguous chiral centers were smoothly prepared under mild conditions (81:19 to 98:2 *exo:endo*, 77-97% *ee* for *exo* product). Currently works is in progress to expand the synthetic utility of the reaction, as well as this catalytic system in other asymmetric transformations.

Experimental Section

General Remarks

NMR data were obtained for ^{1}H at 300, 400 MHz, and for ^{13}C at 50, 75 and 100 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI-HR-MS were recorded on a Bruker Apex-2. Enantiomer ratios were determined by chiral HPLC analysis on a Chiralcel AS column in comparison with authentic racemates. Optical rotation data were determined in CH_2Cl_2 solutions. Column chromatography was performed using silica gel (200–300 mesh). TLC was performed on glass-backed silica plates. Catalysts **1b** and **1c** are commercially available and used as received. Catalysts **1d–g**[18] and substrates **2a–f**[11] were prepared according to the literature procedures. All other reagents were used without purification as commercially available.

General Procedure for [3 + 2] Cycloadditions of Azomethine Imines with α,β-Unsaturated Aldehydes

The α,β-unsaturated aldehyde (0.2 mmol) was added to a mixture of azomethine imine **2** (0.1 mmol), catalyst **1g**·TFA (0.01 mmol) and H_2O (6 μL) in THF (1.0 mL) at 20 °C. The reaction was maintained at this temperature and monitored by TLC analysis. Then the solution was diluted with EtOAc (10 mL), washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed on silica gel eluting with EtOAc/petroleum ether. A portion of the adduct was dissolved in methanol, and excess $NaBH_4$ was added at 0 °C. After 30 min, the corresponding alcohol was extracted with EtOAc, dried (Na_2SO_4), and concentrated for the determination of enantiomeric excess. For **4a**, 85% yield. $[\alpha]_D^{20}$: −43.3 (*c* 1.1, CH_2Cl_2), *exo:endo* 81:19, 96% *ee*. The enantiomeric excess was determined by HPLC on Chiralpak AS column (20% 2-propanol/hexane, 1 mL min^{-1}) after conversion to the alcohol, UV 220 nm, t_{minor} = 19.11 min, t_{major} = 28.23 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (d, J = 2.0 Hz, 1H), 7.42–7.33 (m, 5H), 4.43–4.39 (m, 1H), 4.08 (d, J = 7.2 Hz, 1H), 3.44 (t, J = 7.2 Hz, 1H), 3.15–3.13 (m, 1H), 2.88–2.64 (m, 3H), 1.62 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.6, 164.6, 132.8, 128.9, 128.7, 127.5,

69.2, 66.2, 47.8, 36.4, 29.2, 18.7; IR (CH_2Cl_2): ν = 3749, 3674, 2923, 2851, 1721, 1678, 1456, 1166 cm^{-1}; ESI-HR-MS: m/z = 299.1369, calcd. for $C_{14}H_{16}N_2O_2 + CH_3OH + Na$: 299.1366.

Crystallographic Data

Crystal data for **6** $C_{17}H_{23}ClN_2O_2$ (322.82), orthorhombic, space group $P2_12_12_1$, $a = 9.007(1)$, $b = 9.438(1)$, $c = 20.601(3)$ Å, $U = 1751.36$ (36) $Å^3$, $Z = 4$, specimen $0.54 \times 0.52 \times 0.44$ mm^3, $T = 286(2)$ K, SIEMENS P4 diffractometer, absorption coefficient 0.227 mm^{-1}, reflections collected 4978, independent reflections 4027 [R(int) = 0.0102], refinement by full- matrix least-squares on F^2, data/restraints/parameters 4027/2/212, goodness-of-fit on $F^2 = 0.936$, final R indices [$I > 2\sigma(I)$] $R1 = 0.0375$, $wR2 = 0.0786$, R indices (all data) $R1 = 0.0622$, $wR2 = 0.0839$, largest diff. peak and hole 0.119 and −0.127 e $Å^{-3}$. Crystallographic data for the structure **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-616162. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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[12] The *E*-azomethine imine was formed, see ref.[11a]

[13] The cycloaddition of azomethine imine and α,β-unsaturated aldehyde could occur in the absence of catalyst (< 20% yield in 12 h at ambient temperature).

[14] For recent examples using chiral α,α-diarylprolinol ethers as organocatalysts, see: a) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjarsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; b) Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253–4256; c) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; e) M. Marigo, T. Schulte, J. Franzen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711.

[15] K. Nakano, K. Nozaki, T. Hiyama, *J. Am. Chem. Soc.* **2003**, *125*, 5501–5510.

[16] M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794–797.

[17] *N*-3-Phenylallyl-pyrazolidinone was isolated after reducing the reaction mixture with $NaBH_4$.

[18] C.-Y. Ho, Y.-C. Chen, M.-K. Wong, D. Yang, *J. Org. Chem.* **2005**, *70*, 898–906.

