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Nucleophilic Addition of Grignard Reagents to 3−Acylindoles: Stereoselective Synthesis of Highly Substituted Indoline Scaffolds

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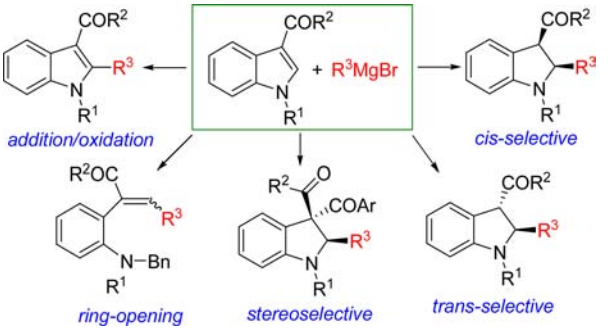
ABSTRACT



3-Acylindoles undergo nucleophilic-type reactions with Grignard reagents to efficiently afford either *cis*- or *trans*-substituted indolines, depending on the different quenching procedures. The enolate intermediate could be trapped by aryl acyl chlorides to provide indolines bearing a quaternary carbon center with high stereoselectivity. In contrast, the use of benzyl bromide as an electrophile results in the fragmentation of the indole ring. The indoline products could be easily transformed into indoles through oxidation with DDQ in a one-pot manner.

The indole ring widely occurs as a key structural subunit in numerous natural products and also represents one of the most important building blocks in organic synthesis.[1] Indoles usually act as nucleophiles to engage in electrophilic substitution reactions, mainly at the C-3 position, due to the π-excessive nature of the indolyl aromatic ring.[2] However, when indoles are substituted with electron-withdrawing groups or there is a leaving group on the indole nitrogen, they can also react with nucleophiles, leading to highly functionalized indole or indoline derivatives.[3] Compared with the well-established electrophilic substitution reactions, much less attention has been paid to nucleophilic-type reactions of indoles. As early as 1962, it was reported that phenylmagnesium bromide adds to 1-methyl- or 1,2-dimethyl-3-benzoylindole to give a Michael adduct of 2,3-substituted indolines.[4] However, only those two examples were examined, and the stereochemical information of the indoline products was not provided. In addition to an acyl substituent, the nitro group has been used to activate the indole ring toward nucleophilic reactions.[5] Gribble et al. showed that addition of the enolates of diethyl malonate to 3-nitro-1-(phenylsulfonyl)-indole forms *trans*-3-nitro-2-substituted indoline.[5c] The studies by Somei's[6] and Gribble's[5d−f] research groups

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(1) For reviews, see: (a) *Indoles*; Sundberg, R. J., Ed.; Academic Press: San Diego, 1996. (b) *Indole Alkaloids*; Rahman, A., Basha, A., Eds.; Harwood Academic: Amsterdam, 1998. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

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(3) (a) Kishbaugh, T. L. S. *Top Heterocycl. Chem.* **2010**, *26*, 117. (b) Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417.

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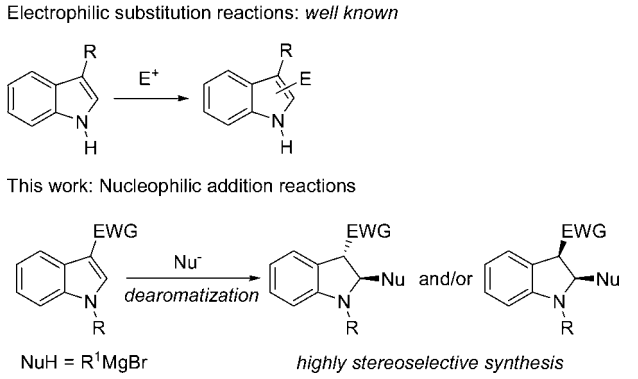
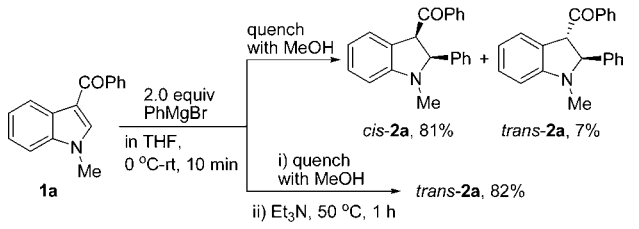
indicated that employing a leaving group such as a 1-hydroxy-, 1-methoxy, or phenylsulfonyl group on the indole nitrogen can facilitate a formal S_N2' reaction to generate substituted free N−H indoles. Although much progress has been achieved in this field, the development of a highly stereoselective process allowing ready access to 2,3-substituted indolines,[5c,7] a ubiquitous scaffold found in natural products and pharmaceutically active compounds,[8] is quite rare. In the course of our studies on indole-based transformations,[9] we accidently found that 3-acyl indoles could react with Grignard reagents in a Michael addition fashion, leading to dearomatization of the indole nucleus and formation of highly substituted indolines with high levels of stereochemical control. In this communication, we describe a general and mild method for stereoselective synthesis of either *trans*- or *cis*-indolines using Grignard reagents, as well as a detailed study for further transformations of the magnesium enolate intermediates with electrophiles (Scheme 1).

Scheme 1



We initially investigated the reaction of 1-methyl-3-benzoylindole **1a** with the commercially available Grignard reagent phenylmagnesium bromide. To our delight, treatment of **1a** with 2.0 equiv of PhMgBr in THF at 0 °C followed by warming to rt and stirring for only 10 min cleanly afforded the *cis*-2-phenyl-3-benzoylindoline **2a** in 81% yield after quenching with MeOH, together with 7% of *trans*-**2a** (Scheme 2).[10] Further optimization of the quenching procedures indicated that when the reaction was first quenched by MeOH, followed by addition of Et_3N and stirring at 50 °C for 1 h, the *cis*-**2a** could convert completely to the *trans*-isomer to afford *trans*-**2a** in 82% yield. Obviously, the *cis*−*trans* isomerization occurs under basic conditions. The results indicated that a high degree of stereoselectivity for both *cis*- and *trans*-diastereomers could be achieved by choosing the appropriate quenching methods. The ^1H NMR shows similar coupling constants of the vicinal protons in *cis*-**2a** and *trans*-**2a** (10.4 and 10.0 Hz, respectively). The stereochemistry of *cis*- or *trans*-indolines **2** was confirmed by X-ray crystal analyses of compounds *cis*-**2g**, *trans*-**2a**, and *trans*-**2e** (*vide infra*).[11]

Scheme 2



The presented procedure via Michael-type addition of Grignard reagents to indoles provides the indoline scaffold in only one step and with high stereoselectivity. Therefore, we were interested in the scope and limitations of this reaction. We first investigated the reactions of PhMgBr with various 3-acylindoles under the conditions for the *trans*-isomers of indoline **2**, and the results are shown in Figure 1. An *N*-benzyl-protected indole reacted smoothly to afford indoline **2b** in 73% yield. The presence of electron-withdrawing groups such as Boc or $CONMe_2$ on the indole nitrogen did not influence the reaction, leading to **2c** and **2d** in 92% and 79% yields, respectively. However, an Ac-protected indole gave **2e** in a lower yield of 58%. The functionality of 5-Br, 5-CN, and 5-BnO on the indole ring could also be incorporated into the reaction procedures, furnishing the Michael adducts **2f**−**2h** in high yields of 84−88%. Especially, the sensitive cyano group was also well tolerated (**2g**). As for carbonyl substituents (R^2) on the acyl moiety, a furanyl or alkenyl group as R^2 was found to be compatible for this reaction (**2i** and **2j**).

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(7) For stereoselective synthesis of indolines by other methods, see: (a) Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J. Org. Chem.* **2008**, *73*, 3040. (b) Hasegawa, K.; Kimura, N.; Arai, S.; Nishida, A. *J. Org. Chem.* **2008**, *73*, 6363. (c) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448. (d) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687. (e) Cera, G.; Crispino, P.; Monari, M.; Bandini, M. *Chem. Commun.* **2011**, *47*, 7803. (f) Nguyen, Q.; Sun, K.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *134*, 7262.

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(10) We found that *cis*-**2a** is not so stable in the air, which can convert to indole slowly. The indole product might be formed through air oxidation. It is recommended column chromatography be performed immediately after the reaction is complete.

(11) X-ray crystal structures of *cis*-**2g**, *trans*-**2a**, *trans*-**2e**, and **4a** are given in the Supporting Information.

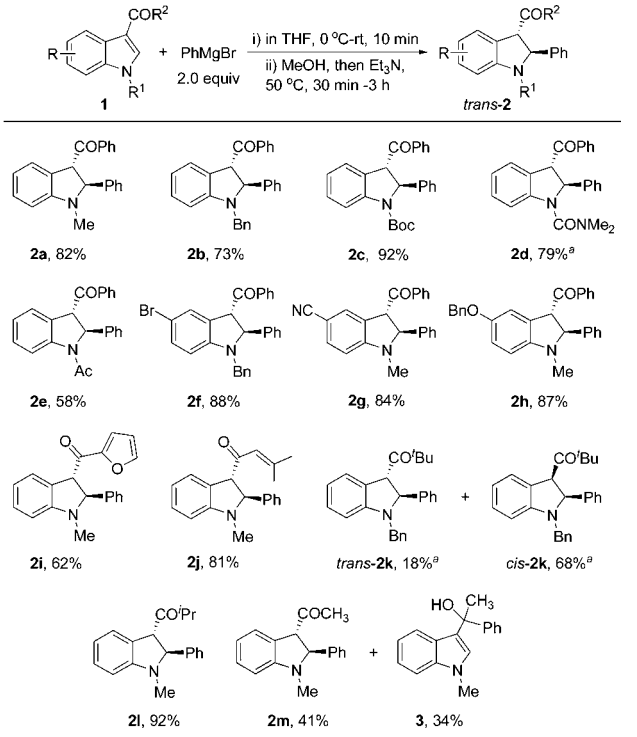

Figure 1. Synthesis of indolines through the reactions with PhMgBr. All yields are isolated yields. [a]Reaction time is 1 h for the first step.

When R^2 is a bulky ^{t}Bu group, a mixture of two diastereomers were obtained, in which *cis*-**2k** was predominant, indicating the *cis* to *trans* isomerization could not complete under the standard reaction conditions. The less hindered ^{i}Pr group (R^2) provided an excellent yield of **2l**. However, the smaller size methyl group as the R^2 substituent gave a mixture of 1,4- and 1,2-adducts (**2m** and **3**), which may be due to the steric and/or electronic effects of the 3-Ac group.

Next, we examined the reactions of 3-acylindoles with various Grignard reagents to produce *trans*-indolines **2**. As shown in Figure 2, a variety of Grignard reagents are compatible with this transformation. Vinyl- as well as substituted vinylmagnesium bromides were suitable nucleophiles, giving rise to **2n** and **2o** in 58−60% yields. Employing ethylmagnesium bromide afforded **2p** in a lower yield of 44%. Aromatic Grignard reagents bearing electron-withdrawing or -donating groups were all proven to be efficient in inducing the nucleophilic addition reaction, and the corresponding *trans*-indolines **2q**−**2s** were obtained in 79−93% yields. In the cases of Grignard reagents with electron-withdrawing groups,[12] the reactions became slower (**2q** and **2r**), probably due to the lower nucleophilicity of these Grignard reagents. Heteroaryl Grignard reagents such as 3-benzothienyl and

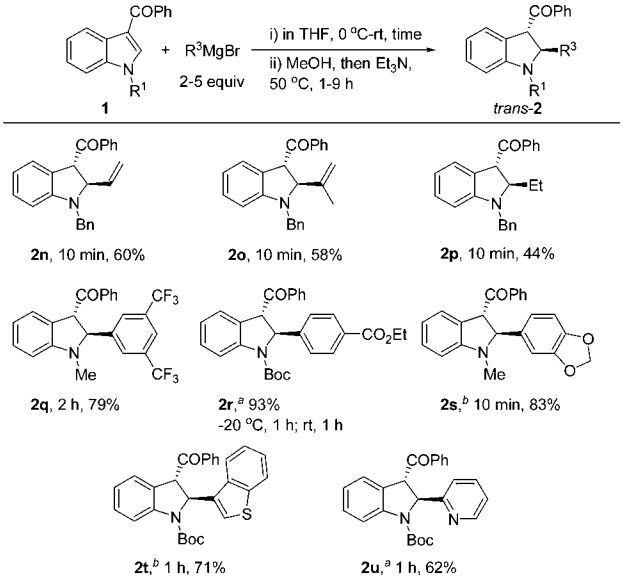

Figure 2. Synthesis of indolines through the reactions with various Grignard reagents. All yields are isolated yields. [a]Grignard reagent was prepared by iodine−magnesium exchange reaction.[12] [b]Grignard reagent was prepared by the reaction of aryl halide with Mg.

2-pyridylmagnesium bromide[12] were also accommodated (**2t** and **2u**).

Under the optimized reaction conditions for *cis*-isomers, *cis*-indolines could also be obtained smoothly. Representative results are shown in Figure 3. In these reactions, only 5−6% of *trans*-isomers were isolated.

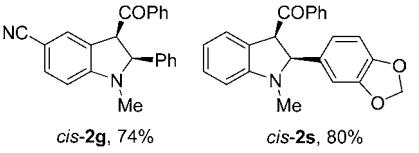

Figure 3. Typical examples for *cis*-indolines **2**.

It is well-known that the enolate intermediates of conjugate addition reactions can be trapped by various electrophiles.[13] We envisioned that the magnesium enolate might be formed in our reaction system, which may react with electrophiles to produce more complex derivatives. Along this line, the magnesium enolate generated by the reaction of **1a** and PhMgBr was trapped with aryl acyl chlorides, giving the corresponding diacyl-indoline products **4** with a quaternary carbon center in good yields (Scheme 3). Interestingly, in all cases, only one diastereomer was formed. The relative stereochemistry is confirmed

(12) (4-(Ethoxycarbonyl)phenyl)magnesium bromide and 2-pyridylmagnesium bromide were prepared by iodine−magnesium exchange reactions; see: (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (b) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 5845.

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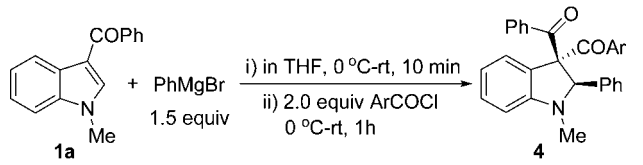
Scheme 3



4a, Ar = *p*-MeC_6H_4, 84%; **4b**, Ar = *p*-ClC_6H_4, 76%
4c, Ar = 2-furanyl, 92%

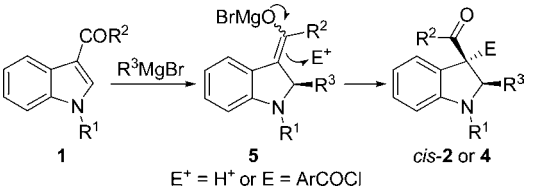
by X-ray crystal analysis of compound **4a**,[11] which clearly shows that the −COAr group derived from acyl chloride and the phenyl group are in a *trans* configuration.

We propose the following mechanism for the observed stereoselectivity (Scheme 4). First, enolate **5** is formed through a nucleophilic addition reaction. Protonation or reaction with electrophiles proceeds preferentially from the less hindered side of **5**, i.e., *trans* to the larger R^3 group, leading to *cis*-**2** or **4**. To our surprise, when benzyl bromide was used as an electrophile, a ring-opening reaction occurred to generate 1,2-difunctionalized benzene **6** in 50% yield as a mixture of alkene isomers (Scheme 5, eq 1). In this case, the enolate intermediate may attack the electrophile through its nitrogen atom, leading to fragmentation of the indole ring. It should be noted that ring-opening reactions of indoles are quite rare.[14] Finally, we tried to apply the method for the synthesis of 2,3-disubstituted indoles in a one-pot procedure. After screening various oxidants, we found that addition of 2.0 equiv of DDQ to the reaction mixture could produce indole **7** in 89% yield (Scheme 5, eq 2).

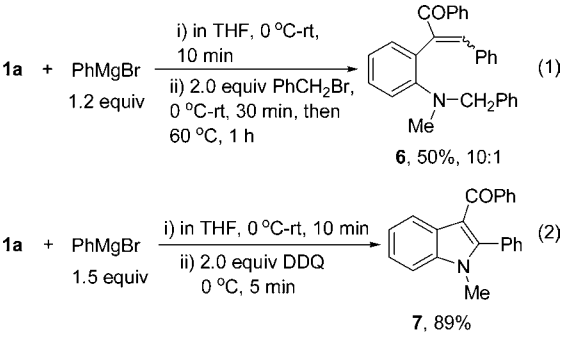
In conclusion, we have developed an efficient process for the stereoselective synthesis of either *cis*- or *trans*-indolines via nucleophilic addition of Grignard reagents to 3-acylindoles. The enolate intermediates could be trapped efficiently by aryl acyl chlorides to afford indolines bearing a quaternary carbon center with high stereoselectivity. The use of benzyl bromide as an electrophile resulted in the ring opening of indoles. In addition, the indoline product could be easily transformed into indoles through oxidation with DDQ in a one-pot manner. The resulting indoline and indole derivatives are attractive building blocks for further synthetic manipulations. Further studies to expand the reaction scope are in progress.

(14) For the fragmentation of indole rings, see: (a) Gribble, G. W.; Saulnier, M. G. *J. Org. Chem.* **1983**, *48*, 607. (b) Johnson, D. A.; Gribble, G. W. *Heterocycles* **1986**, *24*, 2127. (c) Reference 5a, 5b. (d) Kolotaev, A. V.; Belen'kii, L. I.; Kononikhin, A. S.; Krayushkin, M. M. *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 892. (e) Lee, S.; Park, S. B. *Org. Lett.* **2009**, *11*, 5214. (f) Vecchione, M. K.; Sun, A. X.; Seidel, D. *Chem. Sci.* **2011**, *2*, 2178. (g) Knepper, I.; Iaroshenko, V. O.; Vilches-Herrera, M.; Domke, L.; Mkrtchyan, S.; Zahid, M.; Villinger, A.; Langer, P. *Tetrahedron* **2011**, *67*, 5293.

Scheme 4



Scheme 5



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Supporting Information Available. Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compounds *cis*-**2g**, *trans*-**2a**, *trans*-**2e**, and **4a** are given in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.