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A General Catalytic Route to Isoindolinones and Tetrahydroisoquinolines: Application in the Synthesis of (±)-Crispine A

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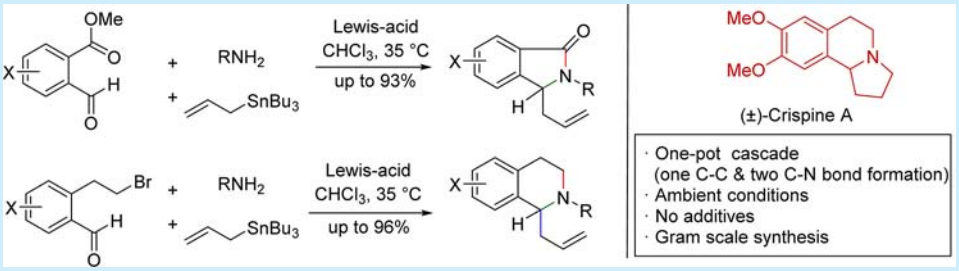
Supporting Information



ABSTRACT: An unprecedented highly efficient Lewis acid catalyzed one-pot cascade has been demonstrated as a general catalytic system for the synthesis of diversely substituted isoindolinones and tetrahydroisoquinolines. The cascade effects one C−C and two C−N bond-forming events in one pot. Several interesting transformations of the products into valuable synthetic intermediates are featured with the successful total synthesis of (±)-crispine A.

Isoindolinone- and tetrahydroisoquinoline-based *N*-heterocyclic scaffolds comprise the key structural feature of a wide range of synthetically and biologically active molecules (**1** and **2**; Figure 1). 3-Alkyl-2,3-dihydro-1*H*-isoindolin-1-ones **1a−d** manifest activities such as antihypertensive,[1] antipsychotic,[2] anti-inflammatory,[3] anesthetic,[4] antiulcer,[5] vasodilatory,[6] antiviral,[7] and antileukemic[8] and are also used in the synthesis of various drugs.[9]

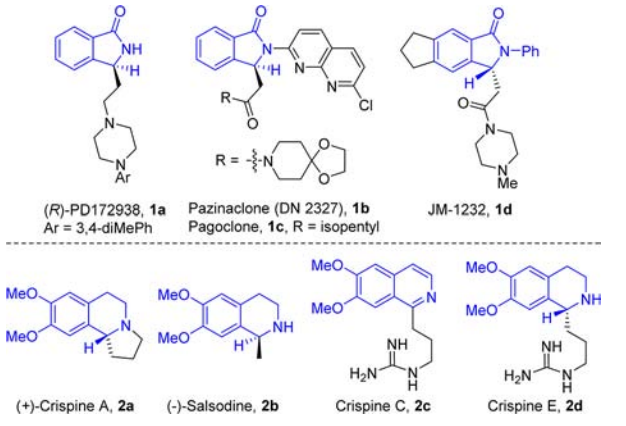
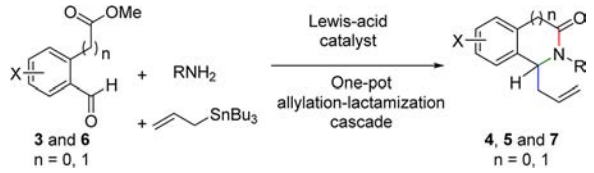


Figure 1. Selected isoindolinones and tetrahydroisoquinolines.

On the other hand, 1-substituted 1,2,3,4-tetrahydroisoquinolines **2a−d** are immensely prominent in diverse biologically active natural products and pharmaceuticals.[10] Although there are several reports in the literature for the synthesis of these compounds[11−13] there exists no precedence to access both of these two important classes of compounds employing a more generalized and common catalytic system in one-pot. To address this, we propose herein a practical approach to isoindolinones and tetrahydroisoquinolinones using a Lewis acid catalyzed one-pot three-component allylation−lactamization cascade of readily available *o*-formyl methyl benzoates and *o*-formyl methyl arylacetates as shown in Scheme 1.[14]

In order to determine what structural parameters affect catalyst performance and to ultimately identify a more efficient catalyst, we performed a systematic optimization of a one-pot three-component allylation−lactamization cascade using various Lewis acids with methyl 2-formyl benzoate (**3a**), *p*-methoxyaniline, and

Scheme 1. Proposed One-Pot Cascade



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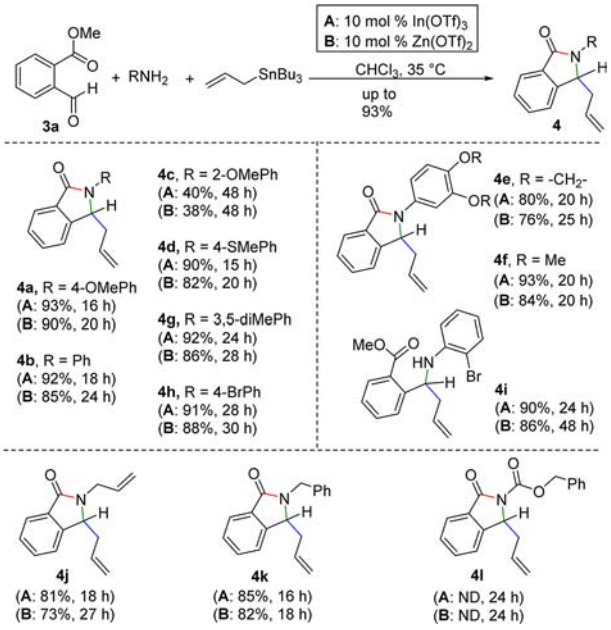
allyltributylstannane (see the Supporting Information for details).

Exhaustive optimization studies in various solvents with different mol % of various metal triflates as Lewis acids (see the Supporting Information for details) at 35 °C indicated that 10 mol % of $Cu(OTf)_2$, $Zn(OTf)_2$, $Sn(OTf)_2$, $Sc(OTf)_3$, and $In(OTf)_3$ afforded allylation−lactamization product **4a** in 88%, 90%, 71%, 68%, and 93% yields, respectively (entries 1−5, Table 1, Supporting Information) in chloroform. Based on these observations, we eventually set forth with two best conditions for further studies viz. 10 mol % of $In(OTf)_3$ (conditions A) and $Zn(OTf)_2$ (conditions B).

Next, a variety of amines were studied under optimized conditions in the allylation/lactamization cascade. To our delight, almost all aromatic amines such as aniline, *o*-methoxyphenyl (OMP), *p*-(thiomethoxy)phenyl (PTMP), 3,4-(methylenedioxy)phenyl, 3,4-dimethoxyphenyl, 3,5-dimethylphenyl, and *p*-bromophenyl afforded the required product **4b−h** in up to 93% yields (Scheme 2) applying conditions A and B. It

Scheme 2. Scope of Reaction with Various Amines[a]



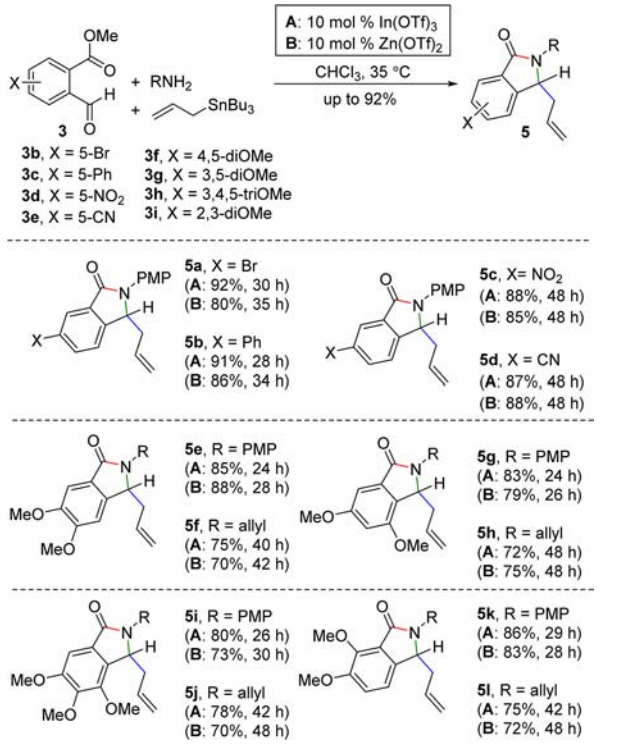
[a]All of the reactions were performed with 1 equiv each of aldehyde, amine, and allyltributylstannane (ratio of 1:1:1.5).

is important to note that isoindolinones with *N*-aryl groups having electron-donating groups (such as **4a** and **4c−f**) can easily be cleaved under oxidative conditions.[15]

In the case of *o*-bromoaniline, instead of the expected isoindolinone, we obtained the uncyclized benzylamine **4i** as a sole product in 86−90% yields. This might be due to the bulky Br-substituent at the *ortho*-position, which hampers the formation of isoindolinone (Scheme 2). This is probably also responsible for an inefficient reaction in the case of *o*-methoxyaniline (see **4c**). Further, we tested easily removable aliphatic amines such as allyl and benzyl for the one-pot cascade. Gratifyingly, isoindolinones **4j−k** having *N*-allyl and *N*-benzyl protecting groups were successfully obtained in 73−85% yields. $CbzNH_2$ as amine source,[16] however, led to a multitude of spots on TLC, indicating nucleophilicity of amines plays a crucial role in the allylation−lactamization cascade.

We then looked forward to the possible substrate scope of our one-pot strategy with diversely substituted *o*-formyl methyl benzoates possessing an entirely different electronic and steric environment. Interestingly, it was found that various *o*-formyl methyl benzoates such as **3b−i** undergo the one-pot cascade without event to afford products **5a−l** in synthetically viable yields (Scheme 3). The X-ray crystal structure of compound **5a** is shown in Figure 2.

Scheme 3. Reaction Scope with Different Substrates



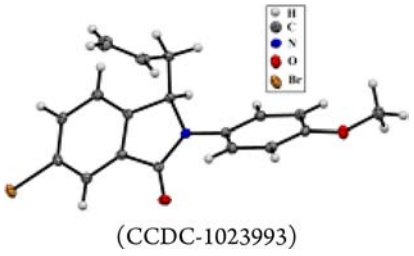


Figure 2. X-ray crystal structure of compound **5a**.

Having secured the synthesis of a wide range of isoindolinones, we next attempted a one-pot, three-component synthesis of isoquinolinones using $PMPNH_2$ as per our hypothesis (Scheme 1) with *o*-formyl methyl arylacetates. However, in this case, the cascade was not facilitated and the reaction stopped at the allylation step to afford solely uncyclized product **8** in excellent yields. Nevertheless, one can utilize amino ester **8** to access a diverse array of tetrahydroisoquinoline alkaloids following a two-step synthetic protocol viz. reduction of ester in the presence of $LiAlH_4$ followed by mesylation and nucleophilic displacement (Scheme 4).[13]

The hunt for a more suitable substrate which could install the tetrahydroisoquinoline skeleton directly in one pot made us see the application of our catalytic protocol on substituted *o*-formylphenethyl bromides **11a−c** (Scheme 5), which may follow

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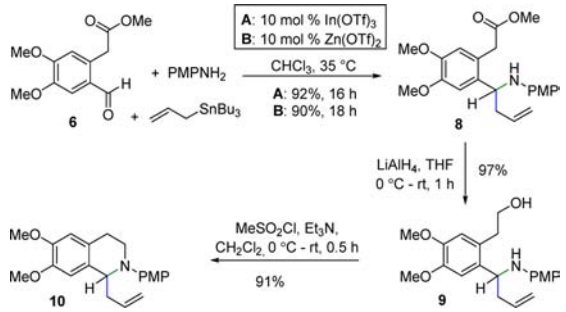
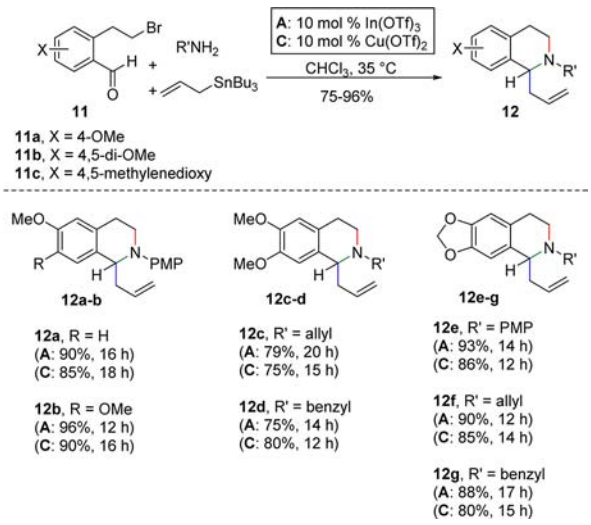
Scheme 4. One-pot three-component allylation of 6



Scheme 5. Scope of Reaction with Various Bromoaldehydes

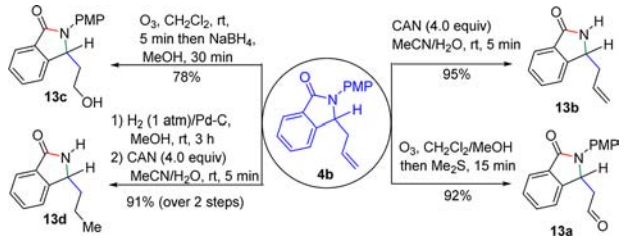


an allylation−*N*-alkylation cascade to effect this cyclization. Interestingly, these aldehydes, when employed in a one-pot, three-component allylation−*N*-alkylation cascade, led to a straightforward access to a variety of *N*-protected tetrahydroisoquinolines in 75−96% yields as shown in Scheme 5. In this process, we found that 10 mol % of $Cu(OTf)_2$ (conditions C) is a better choice than 10 mol % $Zn(OTf)_2$ (conditions B) in addition to 10 mol % of $In(OTf)_3$ (conditions A). In this case also, three different easily removable amines viz. *p*-methoxyaniline, allylamine, and benzylamine were used to ultimately utilize the products for the synthesis of biologically active tetrahydroisoquinoline (THIQ) alkaloids. Under optimized conditions A and C, products **12a−g** were obtained in good to excellent yields (Scheme 5).

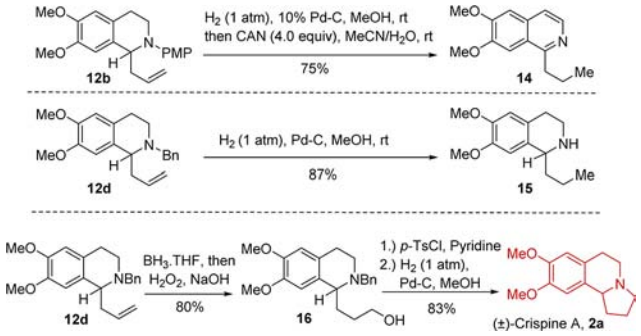
Next, to illustrate the synthetic viability of our methodology, we converted the isoindolinones **4** and tetrahydroisoquinolines **12** into various synthetically useful intermediates. Toward this, the olefinic functionality of the allyl group was converted into an aldehyde and alcohol functionality following ozonolysis and reductive ozonolysis, respectively (see **13a** and **13c**, Scheme 6). The *N*-protecting PMP group of **4b** was oxidatively cleaved using ceric ammonium nitrate (CAN) to afford **13b** in 95% yield (Scheme 6). In another sequence, hydrogenation of the double bond and cleavage of *N*-PMP group afforded **13d** in 91% yield over two steps.

Interestingly, an attempt at oxidative removal of *N*-PMP in the presence of 4.0 equiv of ceric(IV)ammonium nitrate, after hydrogenation of **12b**, led to aromatized isoquinoline moiety **14** (Scheme 7) which could serve as an important synthon for the

Scheme 6. Synthesis of Useful Synthetic Intermediates



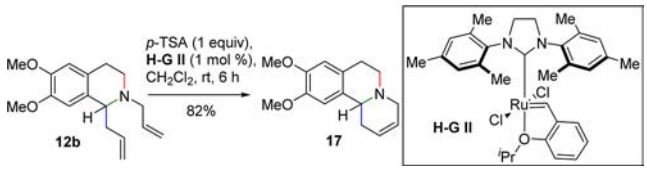
Scheme 7. Total Synthesis of (±)-Crispine A and Related Structures



synthesis of 3,4-dihydroisoquinolinium salts which act as fungicides for treating skin infections.[17] Further, *N*-deprotected tetrahydroisoquinoline **15** was obtained in 87% yield by debenzylation. Eventually, we applied our catalytic protocol in the synthesis of (±)-crispine A[18a] (Figure 1, **2a**) following a three-step sequence viz. hydroboration−oxidation, tosylation, and N-debenzylation-cyclization in overall 66% yield. In addition, compound **16** could serve as an advanced intermediate for the synthesis of crispine C (**2c**) and crispine E (**2d**) after simple synthetic elaboration.[18b]

Further utility of the method has been shown by exploiting the reactivity of the olefinic moiety through ring-closing metathesis (RCM)[19] to construct synthetically useful *N*-heterocycle benzodehydro[*a*]quinolizidine[20] **17** in good yield (Scheme 8).

Scheme 8. Synthetic Elaborations via RCM



In conclusion, we report a highly efficient Lewis acid catalyzed one-pot cascade process for the synthesis of isoindolinones as well as tetrahydroisoquinolines applying a common catalytic route. The reaction is operationally simple and proceeds under mild conditions in high yields. The methodology has been successfully exploited in the synthesis of (±)-crispine A and related structures. The usefulness of the methodology has also been demonstrated by cleavage of *N*-PMP and *N*-benzyl groups and exploiting the unique reactivity of the double bond functionality. Further synthetic exploration toward the enantioselective variant of this strategy is currently under active investigation and will be reported in due course.

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■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and analytical data for all new compounds and crystallographic data file (CIF) for **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor Kankan Bhattacharyya on the occasion of his 60th birthday.

■ REFERENCES

(1) Ferland, J.-M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361.

(2) (a) Linden, M.; Hadler, D.; Hofmann, S. *Hum. Psychopharmacol.* **1997**, *12*, 445. (b) Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157.

(3) Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyano Gongye* **1985**, *16*, 543; *Chem. Abstr.* **1986**, *105*, 6378n.

(4) Laboratori Baldacci, S. P. A. Japanese Patent 5,946,268, 1984; *Chem. Abstr.*, **1984**, *101*, 54922.

(5) Lippmann, W. U.S. Patent 4,267,189, **1981**; *Chem. Abstr.*, **1981**, *95*, 61988m.

(6) Achinami, K.; Ashizawa, N.; Kobayasui, F. Japanese Patent 03,133,955, 1991; *Chem. Abstr.*, **1991**, *115*, 255977j.

(7) (a) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623. (b) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491.

(8) (a) Taylor, E. C.; Zhou, P.; Jenning, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett.* **1997**, *38*, 521.

(9) (a) Riedinger, C.; Endicott, J. A.; Kemp, S. J.; Smyth, L. A.; Watson, A.; Valeur, E.; Golding, B. T.; Griffin, R. J.; Hardcastle, I. R.; Noble, M. E.; McDonnell, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 16038. (b) Boger, D. L.; Lee, J. K.; Goldberg, J.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 1467. (c) Abramovitch, R. A.; Shinkai, I.; Mavunkel, B. J.; More, K. M.; O'Connor, S.; Ooi, G. H.; Pennington, W. T.; Srinivason, P. C.; Stowers, J. R. *Tetrahedron* **1996**, *52*, 3339.

(10) (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. (b) For a review, see: Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341 and references cited therein.

(11) For selected synthesis of isoindolinones, see: (a) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499. (b) Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528. (c) Chen, M.-D.; Zhou, X.; He, M.-Z.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651. (d) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95. (e) Adachi, S.; Onozuka, M.; Yoshida, Y.; Ide, M.; Saikawa, Y.; Nakata, M. *Org. Lett.* **2014**, *16*, 358.

(12) For selected synthesis of tetrahydroisoquinolines, see: (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552. (c) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87. (d) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1295. (e) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143.

(13) (a) Sun, L. X.; Zeng, T.; Jiang, D.; Dai, L.-Y.; Li, C.-J. *Can. J. Chem.* **2012**, 90. (b) Bisai, V.; Suneja, A.; Singh, V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 10737.

(14) For allylation of aldehydes and imines, see: (a) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 1010. (b) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* **2005**, 4217. (c) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (d) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1295. (e) Wei, X. N.; Liu, L. Y.; Wang, B.; Chang, W. X.; Li, J. *Chin. Chem. Lett.* **2009**, *20*, 40. (f) Naodovic, M.; Wadamoto, M.; Yamamoto, H. *Eur. J. Org. Chem.* **2009**, 5129.

(15) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (b) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530.

(16) (a) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005. (b) Beisel, T.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 6046.

(17) (a) Kido, K.; Watainabe, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4964. (b) Jungho, K.; Sangphil, L.; Junyoung, C.; Youngki, P.; Yousuk, L.; Hyungmin, J. *PCT. Int. Appl.* 2006129978, 2006.

(18) (a) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646. (b) Rotte, S. C. K.; Chittiboyina, A. G.; Khan, I. A. *Eur. J. Org. Chem.* **2013**, 6355.

(19) (a) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630. (b) Anand, R. V.; Baktharaman, S.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 3356.

(20) (a) Williams, G. D.; Wadeb, C. E.; Wills, M. *Chem. Commun.* **2005**, 4735. (b) Reddy, N. S. S.; Reddy, B. J. M.; Reddy, B. V. S. *Tetrahedron Lett.* **2013**, *54*, 4228.