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Enantioselective Precipitate of Amines, Amino Alcohols, and Amino Acids via Schiff Base Reaction in the Presence of Chiral Ionic Liquid

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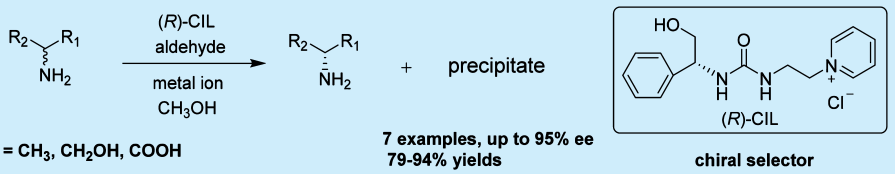
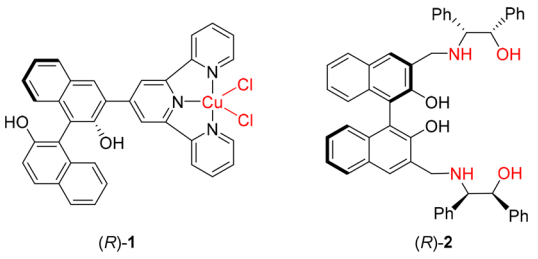
Supporting Information



ABSTRACT: Two novel chiral ionic liquids are synthesized as the chiral selector. Racemates of amines, amino alcohols, and amino acids could generate enantioselective precipitate with multicomponent self-assemblies under mild conditions. The approach allows for enantioseparation with good yields (79−94%) and excellent ee's (>95%).

As highly valuable products, optically pure primary amines play an important role in many fields.[1] Diverse methods have been developed to obtain pure amines such as chromatography,[2] enzymatic catalysis,[3] and kinetic resolution.[4] Meantime, these methods have some disadvantages and remain challenging.[5] As an alternative, enantioselective precipitate has been exploited for a long time. The whole process is convenient and direct even on a large scale. In general, reversible covalent bonds, coordination effects, or hydrogen bonds are necessary for chiral selectors to form stable products with target enantiomers (Scheme 1).[6] However, enantioselective precipitates for racemic amines, amino alcohols, and amino acids with the same selector are rarely reported.[7]

Scheme 1. Reported Chiral Selectors ((*R*)-1 and (*R*)-2) for Enantioselective Precipitate



Chiral ionic liquids (CILs) receive much interest owing to their potential application in asymmetric synthesis,[8] chromatography,[9] spectroscopy,[10] and liquid−liquid extraction.[11] In contrast with common chiral reagents, CILs show strong interactions between the counterions. For example, the hydrogen bond and ionic effect have been found to play a key role in asymmetric synthesis and chiral resolution for products with high excess enantiomer values.[12] Consistent with our interest in the development of chiral resolution, some CILs were synthesized and successfully applied in the enantioseparation of amino alcohols and amino acids.[13] However, only four racemates could be resolved and the method is lacking in generality. It may be due to inadequate stereochemical effect of the chiral ligand.

For the above reasons, we decided to reconstruct the chemical structure of the chiral ionic liquid and develop a novel strategy with multicomponent self-assemblies. In the past, some chiral selectors have been designed and synthesized consisting of aldehyde or carbonyl group, which could react with an amine group through Schiff base reaction.[14] In contrast with the approach, our assumption is that chiral primary amines react with neutral aldehydes to form Schiff base product, which could afford stronger multi-interactions with the chiral ligand.[15]

Herein, as shown in Figure 1, we present new-style CILs as the chiral selector. Derived from (*R*)-phenylglycinol and (*R*)-phenylalaninol, two novel chiral ionic liquids ((*R*)-CIL-**3** and (*R*)-CIL-**4**) composed of a carbamido group and chloridion are synthesized with relatively high yields (Figure S1). The −OH and carbamido group form the strong hydrogen bond with chloridion, which can afford good stereochemical performance. Moreover, these groups are easy to coordinate with the metal ion.

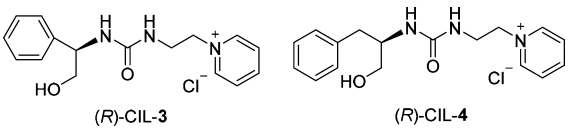


Figure 1. Chemical structures of the new chiral selectors ((*R*)-CIL-**3** and (*R*)-CIL-**4**) for enantioselective precipitate.

The whole procedure contained two steps: a simple reaction between amines and aldehydes, then the formation of

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coordination complex between the chiral ionic liquid and the Schiff base product. As an illustrative example to demonstrate the whole process of enantioselective precipitate, we selected (*rac*)-**5**, (*rac*)-**7** and (*rac*)-**9** as the typical example, respectively (Figure 2).

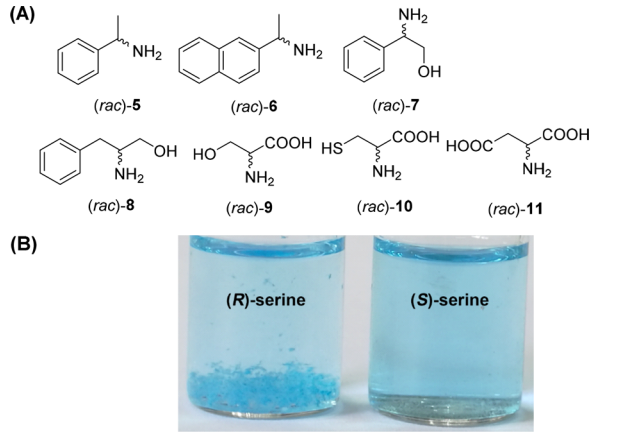

Figure 2. (A) Structures of amines, amino alcohols, and amino acids. (B) Photographs of (*R*)-CIL-**3** treated with (*R*)-serine and (*S*)-serine via multicomponent self-assemblies.

For 1-phenylethylamine, as we can see from Table S1, different parameters including aldehydes, reaction temperature, and metal salts were systematically studied. Namely, as shown in Figure 3, (*R*)-CIL-**3** (0.1 mmol) + $CoCl_2$ (0.1 mmol) could

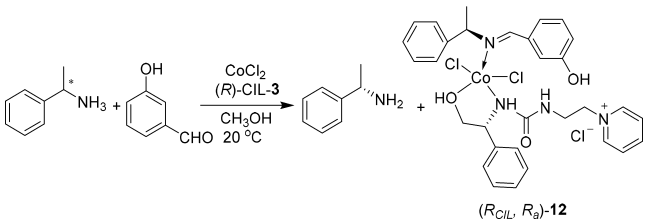

Figure 3. Multicomponent reaction of (*rac*)-5,3-hydrobenzaldehyde, (*R*)-CIL-**3** and $CoCl_2$.

form a coordinated complex with the Schiff base derived from (*R*)-**5** (0.1 mmol) and 3-hydroxybenzaldehyde (0.105 mmol) in CH_3OH. The results indicated that the aldehyde played a vital role in the whole process. Only the hydroxyl group in the 3-position of benzaldehyde was successfully examined with this method. The whole reaction completed in nearly 2 h at 20 °C, which could obtain the yield of 79% with 95% ee. On the other hand, the separation efficiency for amines obtained by using (*R*)-CIL-**4** was lower than that of (*R*)-CIL-**3**. Besides that, it should be noted that (*S*)-**5** would form precipitate when the temperature raised to 40 °C. It showed that the whole process was thermodynamic controlled. Thus, 20 °C was selected as the optimized temperature for amines.

For serine and 2-phenylglycinol, similar to chiral resolution of amines, optimization of reaction parameters was discussed in detail (Table S2). As shown in Figure 4, (*R*)-**9** (0.1 mmol) could easily react with 3-formylindole (0.105 mmol) to produce the Schiff base in CH_3OH/H_2O (v/v = 4/1). Then, the product generated the coordinated complex with (*R*)-CIL-**3** (0.1 mmol) and $CuCl_2$ (0.1 mmol). The whole reaction completed in nearly 24 h with excellent yield (94%) (Figure

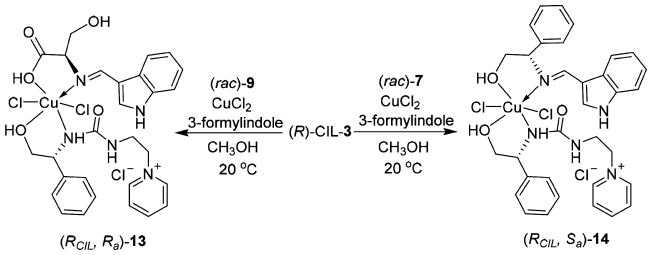

Figure 4. Multicomponent reaction of (*rac*)-7 ((*rac*)-**9**), 3-formylindole, (*R*)-CIL-**3**, and $CuCl_2$.

2B). When the temperature gave rise from 20 to 40 °C, the reaction time did not show much difference. Moreover, (*R*)-**9** could not react with the ligand even at 40 °C in 24 h. It indicated that the process was not thermodynamically controlled.

In contrast, under the same conditions, (*S*)-**7** could form the coordinated complex with (*R*)-CIL-**3** in 2 h. Compared to amino acids, the chemical bonding between the chiral ligand and amino alcohols was similar. The −OH side group of serine was also involved in binding, which led to different configurations of the complex. The chemical yield for (*S*)-**7** was 91%.

Having obtained optimized reaction conditions, we probed the generality of other racemates by enantioselective precipitate in the next step. Four amines and amino alcohols (Table 1,

Table 1. Investigation of the Substrate Scope[a]

entry	CIL	racemates	ee (%)	yield (%)	time (h)
1	(*R*)-CIL-**3**[f]	(*rac*)-**5**	>95[b]	79	2[d]
2	(*R*)-CIL-**3**[f]	(*rac*)-**6**	>95[b]	88	2[d]
3	(*R*)-CIL-**3**[g]	(*rac*)-**7**	>95[c]	91	2[d]
4	(*R*)-CIL-**3**[g]	(*rac*)-**8**	>95[c]	86	2[d]
5	(*R*)-CIL-**3**[g]	(*rac*)-**9**	>95[b]	94	24[d]
6	(*R*)-CIL-**3**[g]	(*rac*)-**10**	>95[b]	91	5[e]
7	(*R*)-CIL-**3**[g]	(*rac*)-**11**	>95[c]	91	2[e]

[a]Reaction conditions: 0.1 mmol scale of (*R*)-CIL-**3**, 0.1 mmol scale of substrate, 0.1 mmol of metal salt, 0.105 mmol aldehyde, and 1 mL of CH_3OH except amino acids in CH_3OH/H_2O (v/v = 4/1). ee's are determined by the weight ratio of the precipitate. [b]$(C_{(R,R)} - C_{(R,S)})/(C_{(R,R)} + C_{(R,S)})$. [c]$(C_{(R,S)} - C_{(R,R)})/(C_{(R,S)} + C_{(R,R)})$. [d]The reaction was at 20 °C. [e]The reaction was at 40 °C. [f]$CoCl_2$. [g]$CuCl_2$.

entries 1−4) in this series were successfully isolated with one configuration in the range of 79−91% yields. As shown in entries 5−7, the β-position chain of amino acids with proton groups such as −OH, −SH, and −COOH gave products with high yields in the 91−94% range and ee's >0.95. Besides that, we found an interesting outcome for aspartic acid (*rac*-**11**). (*S*)-**11** was apt to produce precipitate with (*R*)-CIL-**3** within 2 h in 40 °C, which was isolated in 91% yield. Meantime, (*R*)-**11** could also afford the product with (*R*)-CIL-**3** under 24 h. These results indicated that the enantioselective formation of the coordinative complex was a competitive reaction.

Considering the C═N group is sensitive to acidic medium, the disassembly procedure presented in Figure 5 is also convenient under mild conditions. Furthermore, the chiral ionic liquid dissolved in water or methanol only was recycled conveniently through extraction. According to these characteristics, chiral ionic liquids could be recycled in quantitative yield.

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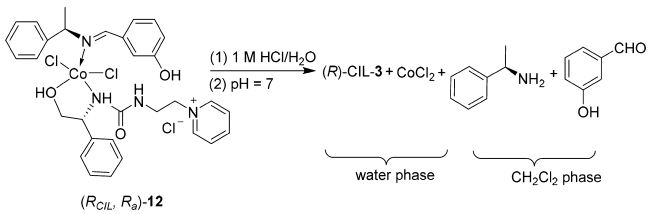

Figure 5. Disassembly of (R_{CIL}, R_a)-12 and the recycle of (*R*)-CIL-3.

Due to the insolubility of the precipitate in solvents, FTIR spectra, DFT calculations (at the B3LYP/3-21G* level using the Gaussian 03 program package[16]), and ^{1}H NMR spectra are used to establish possible structures of the coordination complex. From the FTIR spectrum of (R_{CIL},R_a)-**13**, CIL-**3**, and *rac*-**9** (Figure S2), the stretching vibration of the carbamido group red shifts from 1667 to 1558 cm^{-1}. The stretching vibration of C═N also red shifts. The stretching vibration of C−O blue shifts from 1132 to 1205 cm^{-1}. It indicates the coordination bond among −OH and ureido of (*R*)-CIL-**3** and C═N and −COOH of serine.

As shown in Figure 6, we display energy-optimized structures of (R_{CIL},R_a)-**13**−H_2O* and (R_{CIL},S_a)-**13**−H_2O*. In (R_{CIL},R_a)-

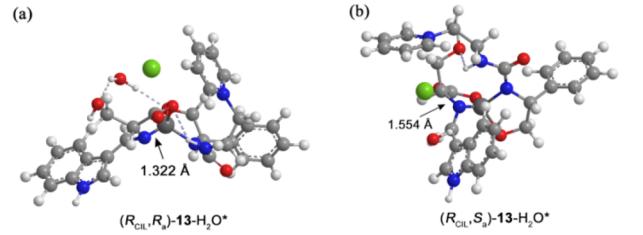

Figure 6. Energy-optimized structures of (a) (R_{CIL},R_a)-**13**−H_2O* and (b) (R_{CIL},S_a)-**13**−H_2O* obtained by DFT calculations. Dotted lines indicate hydrogen bonds.

13−H_2O*, multiple hydrogen bonds around the hydrone and −OH belonging to (*R*)-CIL-**3** and serine promote stability of the coordinative complex. In contrast, the intermolecular hydrogen bond between −NH of ureido and −OH of Schiff base product restricts the freedom of the C═N bond. It could bring enhanced steric hindrance between the indole ring and pyridinium cation, especially in (R_{CIL},S_a)-**13**−H_2O*. As a result, the bond distance of coordination bonds formed with Cu(II) and C═N bond is much different (1.322 vs 1.554 Å). Calculations predict that the coordination bond of (R_{CIL},R_a)-**13**−H_2O* is more stable than that of (R_{CIL},S_a)-**13**−H_2O* by 7.3 kcal/mol. Furthermore, optimized structures of (R_{CIL},S_a)-**14** and (R_{CIL},R_a)-**14** are also obtained by DFT calculations (Figure S3). Unfortunately, DFT calculations do not perform reasonable energy-optimized structure of (R_{CIL},R_a)-**12**. Alternatively, as shown in Figure S4B, partial ^{1}H NMR signals of the pyridinium cation moiety up-shift 0.18 ppm once the the product is formed. It verified the electrostatic interaction between pyridinium cation and chloridion, which contributed to the improvement of enantioselectivity.

To conclude, this work demonstrates an approach to an enantioselective precipitate via multicomponent self-assemblies. Namely, the product of Schiff base coordinated with the novel chiral ionic liquid in the presence of metal ions. (*R*)-CIL-**3** shows high enantioselectivities and a wide scope toward amines, amino alcohols, and amino acids. The whole process could be realized even on a large scale (5 g). Above all, we believe that this work may open the way for the use of chiral ionic liquids in enantioseparation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01935.

Experimental details, characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Books: (a) Lough, W. J.; Wainer, I. W. *Chirality in Natural and Applied Science*; Blackwell: Oxford, UK, 2002. (b) Francotte, E.; Lindner, W. *Chirality in Drug Research*; Wiley-VCH: Weinheim, 2006. (c) Nugent, T. C. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, 2010.

(2) Chromatography: (a) Hoffmann, C. V.; Laemmerhofer, M.; Lindner, W. *J. Chromatogr. A* **2007**, *1161*, 242−251. (b) Sun, P.; Armstrong, D. W. *J. Chromatogr. A* **2010**, *1217*, 4904−4918. (c) Stringham, R. W. *J. Chromatogr. A* **2005**, *1070*, 163−170. (d) Hyun, M. H.; Han, S. C.; Lipshutz, B. H.; Shin, Y. J.; Welch, C. J. *J. Chromatogr. A* **2002**, *959*, 75−83.

(3) Enzymatic catalysis: (a) Abrahamson, M. J.; Wong, J. W.; Bommarius, A. S. *Adv. Synth. Catal.* **2013**, *355*, 1780−1786. (b) Asano, Y.; Nakazawa, A.; Endo, K.; Hibino, Y.; Ohmori, M.; Numao, N.; Kondo, K. *Eur. J. Biochem.* **1987**, *168*, 153−159. (c) Abrahamson, M. J.; Vázquez-Figueroa, E.; Woodall, N. B.; Moore, J. C.; Bommarius, A. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3969−3972. (d) Koszelewski, D.; Lavandera, I.; Clay, D.; Guebitz, G. M.; Rozzell, D.; Kroutil, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 9337−9340.

(4) Kinetic resolution: (a) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060−17061. (b) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624−13526. (c) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885−888. (d) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001. (e) Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011−3030.

(5) (a) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788−824. (b) Synoradzki, L.; Bernas, U.; Ruskowski, P. *Org. Prep. Proced. Int.* **2008**, *40*, 163−200.

(6) Enantioselective precipitate: (a) Tripathi, A.; Kumar, A.; Pandey, P. S. *Tetrahedron Lett.* **2012**, *53*, 5745−5748. (b) Liu, H. L.; Hou, X. L.; Pu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 382−385. (c) He, X.; Zhang, Q.; Wang, W.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2011**, *13*, 804−807. (d) Chen, X.; Huang, Z.; Chen, S. Y.; Li, K.; Yu, X. Q.; Pu, L. *J. Am. Chem. Soc.* **2010**, *132*, 7297−7299.

(7) (a) Zheng, Y. S.; Ran, S. Y.; Hu, Y. J.; Liu, X. X. *Chem. Commun.* **2009**, 1121−1123. (b) Wang, C.; Wu, E.; Wu, X.; Xu, X.; Zhang, G.; Pu, L. *J. Am. Chem. Soc.* **2015**, *137*, 3747−3750.

DOI: 10.1021/acs.orglett.7b01935
Org. Lett. XXXX, XXX, XXX−XXX

(8) Chiral ionic liquids used in asymmetric synthesis: (a) Luo, S.; Zhang, L.; Mi, X.; Qiao, Y.; Cheng, J. P. *J. Org. Chem.* **2007**, *72*, 9350−9352. (b) Gauchot, V.; Schmitzer, A. R. *J. Org. Chem.* **2012**, *77*, 4917−4923. (c) Ni, B.; Zhang, Q.; Dhungana, K.; Headley, A. D. *Org. Lett.* **2009**, *11*, 1037−1040. (d) Obregón-Zúñiga, A.; Milán, M.; Juaristi, E. *Org. Lett.* **2017**, *19*, 1108−1111.
(9) Chiral ionic liquids used in chromatography: (a) Zhou, Z.; Li, X.; Chen, X.; Hao, X. *Anal. Chim. Acta* **2010**, *678*, 208−214. (b) Huang, X.; Luckey, J. A.; Gordon, M. J.; Zare, R. N. *Anal. Chem.* **1989**, *61*, 766−770. (c) Yanes, E. G.; Gratz, S. R.; Baldwin, M. J.; Robison, S. E.; Stalcup, A. M. *Anal. Chem.* **2001**, *73*, 3838−3844. (d) Rizvi, S. A.; Shamsi, S. A. *Anal. Chem.* **2006**, *78*, 7061−7069.
(10) Chiral ionic liquids used in spectroscopy: (a) Clavier, H.; Boulanger, L.; Audic, N.; Toupet, L.; Mauduit, M.; Guillemin, J. C. *Chem. Commun.* **2004**, 1224−1225. (b) Grabolle, M.; Spieles, M.; Lesnyak, V.; Gaponik, N.; Eychmüller, A. *Anal. Chem.* **2009**, *81*, 6285−6294.
(11) Chiral ionic liquids used in liquid−liquid extraction: (a) Tang, F.; Zhang, Q.; Ren, D.; Nie, Z.; Liu, Q.; Yao, S. *J. Chromatogr. A* **2010**, *1217*, 4669−4674. (b) Wu, D.; Zhou, Y.; Cai, P.; Shen, S.; Pan, Y. *J. Chromatogr. A* **2015**, *1395*, 65−72.
(12) González, L.; Altava, B.; Bolte, M.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V. *Eur. J. Org. Chem.* **2012**, *2012*, 4996−5009.
(13) Wu, D.; Yin, Q.; Cai, P.; Zhao, X.; Pan, Y. *Anal. Chim. Acta* **2017**, *962*, 97−103.
(14) Reported chiral ligands: (a) Park, H.; Kim, K. M.; Lee, A.; Ham, S.; Nam, W.; Chin, J. *J. Am. Chem. Soc.* **2007**, *129*, 1518−1519. (b) Huang, H.; Nandhakumar, R.; Choi, M.; Su, Z.; Kim, K. M. *J. Am. Chem. Soc.* **2013**, *135*, 2653−2658. (c) Takeda, R.; Kawamura, A.; Kawashima, A.; Sato, T.; Moriwaki, H.; Izawa, K.; Akaji, K.; Wang, S.; Liu, H.; Aceña, J. L.; Soloshonok, V. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 12214−12217. (d) De los Santos, Z. A.; Wolf, C. *J. Am. Chem. Soc.* **2016**, *138*, 13517−13520. (e) Soloshonok, V. A.; Ellis, T. K.; Ueki, H.; Ono, T. *J. Am. Chem. Soc.* **2009**, *131*, 7208−7209.
(15) Shcherbakova, E. G.; Minami, T.; Brega, V.; James, T. D.; Anzenbacher, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 7130−7133.
(16) DFT calculations: (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.

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Org. Lett. XXXX, XXX, XXX−XXX