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Brucine Diol–Copper-Catalyzed Asymmetric Synthesis of *endo*-Pyrrolidines: The Mechanistic Dichotomy of Imino Esters

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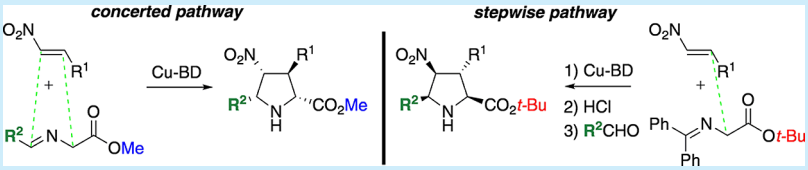
Supporting Information

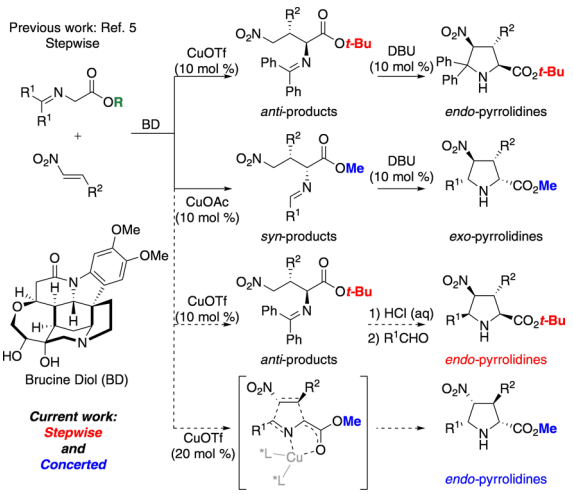


ABSTRACT: Enantio- and diastereodivergent approaches to pyrrolidines are described by using catalyst- and substrate-controlled reaction pathways. A concerted *endo*-selective [3 + 2]-cycloaddition pathway is developed for the reaction of methyl imino ester, whereas *endo*-pyrrolidines with an opposite absolute stereochemical outcome are prepared by using the stepwise reaction pathway of *tert*-butyl imino ester. The development of catalyst- and substrate-controlled stereodivergent approaches highlights the inherent substrate–catalyst interactions in the [3 + 2]-cycloaddition reactions of metalated azomethine ylides.

Chiral pyrrolidines are one of the key structural motifs present in many biologically important compounds[1] as well as in the core structures of fascinating organocatalysts.[2] Among the synthetic strategies developed for chiral pyrrolidines, the catalytic asymmetric [3 + 2]-cycloaddition reactions between in situ generated azomethine ylides and activated alkenes render a facile access to pyrrolidines with a diverse array of functional groups.[3] Chiral metal catalysts as well as organocatalysts have been investigated in which the absolute and relative stereochemistries of products are primarily controlled by specific chiral ligand sets. However, the relationship between the stereochemical outcome and the reaction pathway of [3 + 2]-cycloaddition reactions of imino esters with activated alkenes are not well understood due to the lack of clear experimental evidence for either concerted or stepwise reaction pathway.[4]

Recently, we disclosed a diastereodivergent conjugate addition reaction of imino esters to nitroalkenes in the presence of brucine diol (BD)–Cu complexes (Scheme 1).[5] Our substrate-controlled diastereoselective conjugate addition reactions shed light on the mechanistic insight into the *stepwise exo*- and *endo*-selective [3 + 2]-cycloaddition reaction pathways of imino esters with nitroalkenes.[6] With the aim of further studying the reaction mechanisms of [3 + 2]-cycloaddition reactions, we investigated the absolute and relative stereochemical outcomes of pyrrolidines from imino esters and nitroalkenes under the BD–Cu catalysis. Herein, we present an *endo*-selective *concerted* [3 + 2]-cycloaddition reaction between imino esters and nitroalkenes, ultimately leading to the discovery of the reaction pathway-controlled enantiodivergent and the substrate-controlled diastereodivergent [3 + 2]-cycloaddition reactions of azomethine ylides.

Scheme 1. Enantiodivergent Pyrrolidine Syntheses: Stepwise and Concerted Reaction Pathways



First, we reexamined the [3 + 2]-cycloaddition reactions between methyl imino ester **1** and nitroalkene **2** using various BD–Cu catalysts (Table 1). Since the use of BD–Cu catalysts derived from CuOAc exclusively led to the formation of *syn*-conjugate addition product,[5] we opted for the use of other copper salts that typically require amine bases for the generation of active BD–Cu catalysts.[7] The change of copper salts dramatically changed the course of the reaction, leading to the formation of a mixture of pyrrolidines instead of conjugate

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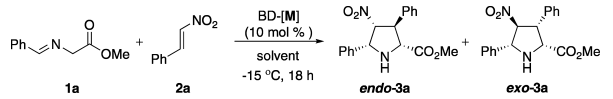
Table 1. Optimization of *Endo*-Selective [3 + 2]-Cycloaddition Reaction



entry	metal/base	solvent	*endo*/*exo*[a]	yield[b] (%)	ee[c] (%)
1	$CuCl/Et_3N$	THF		NR	
2[d]	$CuCl/Et_3N$	TCE	25:1	55	72
3	CuI/Et_3N	THF	3:1	20	50
4	$CuOTf/Et_3N$	THF	4:1	65	28
5	CuOTf/DBU	THF	10:1	61	77
6	CuOTf/DBN	THF	13:1	57	82
7	CuOTf/DBN	2-MeTHF	9:1	67	66
8	CuOTf/DBN	$PhCH_3$		NR	
9	CuOTf/DBN	$CHCl_3$	20:1	65	77
10	$Cu(OTf)_2$/DBN	THF	7:1	64	80
11	$Cu(NTf_2)_2$/DBN	THF	10:1	94	80
12[e]	CuOTf/DBN	THF	1:1	85	26
13[f]	CuOTf/DBN	THF	25:1	97	84

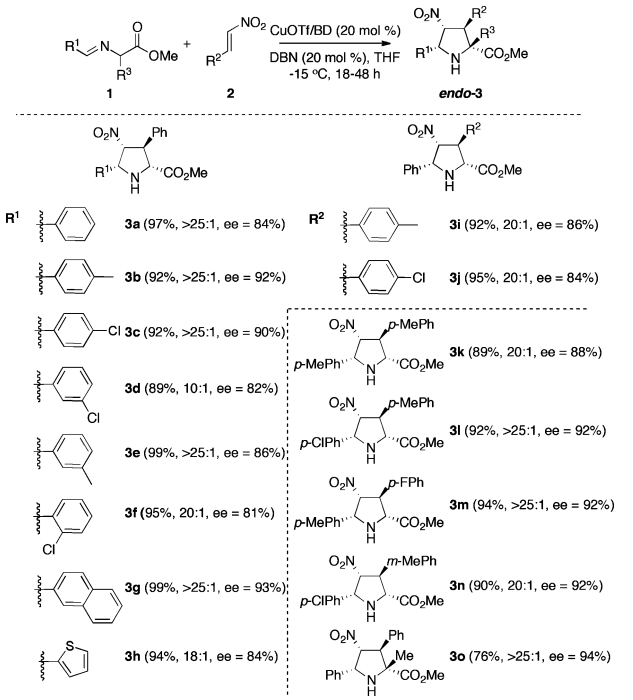
[a]Determined by crude ^1H NMR. [b]Isolated yield of products after column chromatography. [c]Determined by HPLC using a chiral column. [d]20 mol % of EtOH additive. [e]Reaction at 0 °C. [f]20 mol % of BD-CuOTf. NR = no reaction.

addition products (Table 1, entries 1−4). Thus, the use of CuCl in 1,1,2-trichloroethane preferentially provided *endo*-**3a** in 72% ee (Table 1, entry 2). However, no further improvement in the reactivity and selectivity was made when other reaction parameters were varied. Gratifyingly, when we employed CuOTf in combination with DBN as base the formation of *endo*-**3a** improved to 82% ee with 13:1 dr (Table 1, entry 6). No significant solvent effect was found (Table 1, entries 7−9). The oxidation state of copper did not have much influence on the observed stereoselectivities (Table 1, entries 10 and 11); however, the use of either $Cu(NTf_2)_2$ or elevated reaction temperature showed a much faster reaction albeit with diminished selectivities (entries 11 and 12). Finally, the catalyst loading was investigated to improve the reactivity and selectivity, and the use of 20 mol % of BD−CuOTf was identified as an optimal condition, leading to the formation of *endo*-**3a** in 97% yield with 84% ee (Table 1, entry 13).

The optimized *endo*-selective [3 + 2]-cycloaddition conditions were further investigated using other imino esters and nitroalkenes (Scheme 2). A wide range of imino esters with different electronic and steric effects provided the desired *endo*-**3a**−**h** in high yields with good to excellent enantio- as well as diastereoselectivities.[8] The reaction was also applicable to other nitroalkenes with slightly diminished enantioselectivities (*endo*-**3i**−**j**); however a general trend in the substrate−selectivity relationship was not found since a combination of different substituents on the imino esters and the nitroalkenes provided excellent selectivities (*endo*-**3k**−**o**). The relative and absolute stereochemistry of *endo*-**3** was confirmed to be (2*R*,3*S*,4*R*,5*R*) by comparison of its HPLC retention times with authentic samples (see the Supporting Information for details).

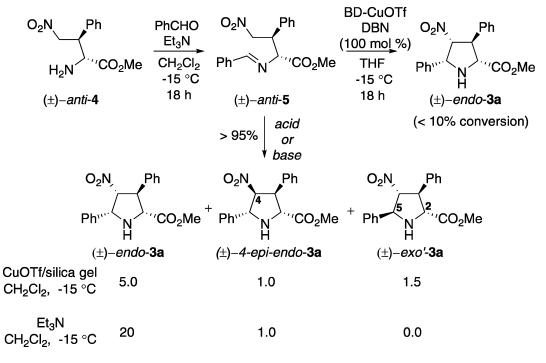
The stereochemical outcome of the *endo*-selective [3 + 2]-cycloaddition reaction provided insightful mechanistic information. Upon close inspection of varied reaction conditions in Table 1 and Scheme 2, we observed the *exclusive* formation of *endo*-**3** and *exo*-**3** regardless of the reaction conversion. The absence of conjugate addition products as well as other diastereomeric pyrrolidines suggested a strong possibility of a

Scheme 2. Scope of *Endo*-Selective [3 + 2]-Cycloaddition Reaction



concerted [3 + 2]-cycloaddition pathway. To further verify such a mechanistic pathway, we independently prepared the Mannich precursor *anti*-**5** (vide infra). Upon subjecting the Mannich precursor to a stoichiometric amount of BD−CuOTf catalysts, a slow formation of *endo*-**3a** was observed (Scheme 3). The

Scheme 3. Pyrrolidines from Intramolecular Mannich Reaction Pathway



inefficient intramolecular Mannich cyclization of *anti*-**5** under our asymmetric conditions strongly implied a less likely scenario for the stepwise reaction pathway to *endo*-**3a**. In addition, the intramolecular Mannich reaction of *anti*-**5** under acidic conditions resulted in a 5:1:1.5 mixture of three pyrrolidines. This result further strengthened the possible formation of other diastereomeric pyrrolidines through a stepwise reaction mechanism. Under basic conditions, however, the stereoselective intramolecular Mannich reaction was observed to provide *endo*-**3a**.

The stereochemical outcome of the *concerted* [3 + 2]-cycloaddition reactions depicted in Scheme 2 was opposite to the *endo*-pyrrolidines obtained through a sequence of *anti*-selective conjugate addition and Mannich cyclization. To further

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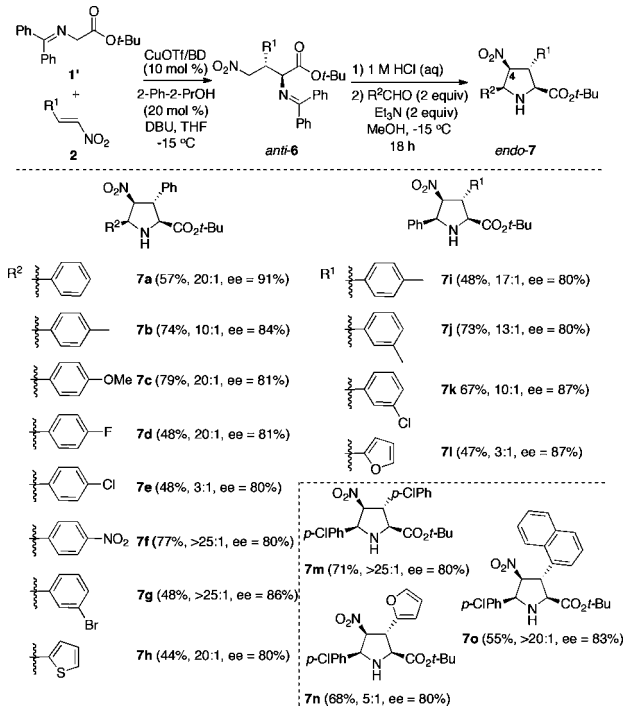
investigate the *stepwise* approach to *endo*-pyrrolidines, we examined the Mannich cyclization of chiral *anti*-**6** (Scheme 4).

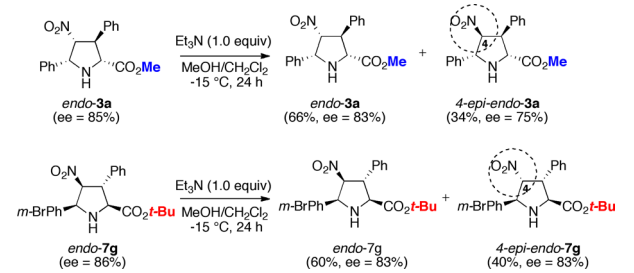
Scheme 4. Scope of Stepwise Approach to *endo*-7



The removal of a benzophenone imine moiety followed by condensation with aldehydes led to the stereoselective formation of *endo*-7 in good to excellent yields (see the Supporting Information for details). In all cases, the formation of minor 4-*epi*-*endo*-7 was observed while no other diastereomeric pyrrolidines were detected. While the observed diastereoselectivity of *endo*-7 varied among substrates (dr >25:1 to 3:1), a synthetically useful level of enantioselecivity was obtained using a range of nitroalkenes and aldehydes (80−90% ee's). The relative and absolute stereochemistry of *endo*-7 was unambiguously confirmed to be (2*S*,3*R*,4*S*,5*S*), a stereochemical outcome opposite to that of the *endo*-**3** from the *concerted* [3 + 2]-cycloaddition reaction pathway.[9]

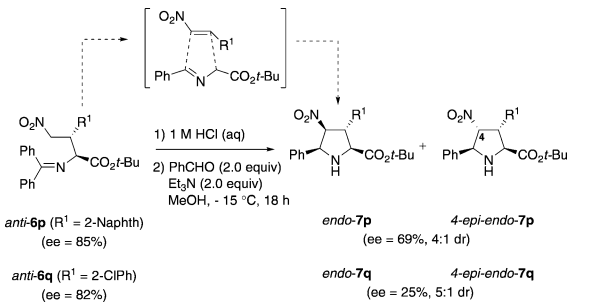
In an effort to identify the origin of 4-*epi*-*endo*-pyrrolidines, we reacted enantioenriched *endo*-pyrrolidines under basic conditions (Scheme 5). Based on the formation of *endo*- and 4-*epi*-*endo*-pyrrolidines in comparable enantioselectivities, we concluded that the 4-*epi*-*endo*-pyrrolidines likely originated from the epimerization of *endo*-pyrrolidines under basic conditions in protic solvent, MeOH, a possible cause for varied diastereoselectivities of *endo*-7 via the *stepwise* reaction sequence. Also, the fact that the formation of 4-*epi*-*endo*-**3** was not observed in our *concerted* [3 + 2]-cycloaddition conditions indicated that the epimerization did not occur under the Cu−BD-catalyzed asymmetric conditions.

Scheme 5. Epimerization of *endo*-Pyrrolidines



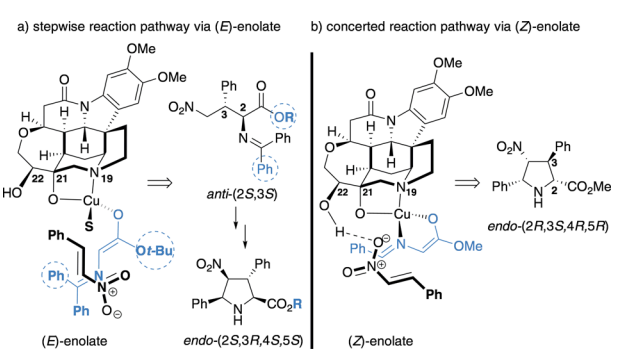
The observed enantioselectivities of *endo*-7 from the stepwise reaction sequence in Scheme 4 were lower than those of conjugate addition products, *anti*-**6**. For example, rather surprisingly, some conjugate addition products, *anti*-**6p** and *anti*-**6q**, displayed a more significant loss of enantioselectivity under the base-promoted intramolecular Mannich cyclization conditions (Scheme 6). The erosion of enantioselectivity of *endo*-7 suggested that the Mannich precursors, *anti*-**6**, underwent a retro-Michael reaction. However, the fact that no other diastereomeric pyrrolidines were observed clearly illustrated that the recombination occurred without a significant dissociation of nitroalkenes and imino esters. The reversible nature of the Mannich precursors, *anti*-**6**, implies the difficulty associated with the development of *endo*-selective catalytic asymmetric [3 + 2]-cycloaddition reactions of imino esters and nitroalkenes. Thus, it is conceivable that the observation of low diastereo- and enantioselectivities of *endo*-pyrrolidines in literature could be due to the reversible nature of Mannich intermediates like *anti*-**5**/**6** in a stepwise reaction pathway.[10]

Scheme 6. Reversibility of Mannich Precursors



While more work is needed to assert the reaction mechanisms, the specific substrate-catalyst interaction is believed to be a crucial diverging factor for the *endo*-selective *concerted* [3 + 2]-cycloaddition and conjugate addition reactions. Thus, the stereochemical outcome of the BD-Cu-catalyzed reactions between methyl imino ester and nitroalkenes could be explained by invoking the stereoselective generation of enolates (Scheme 7).[11] The *O*-metalated enolate of *tert*-butyl glycine imines should favor a (*E*)-geometry with a coordinating species (THF or protic additives) at the copper center, whereas a (*Z*)-geometry could be

Scheme 7. Stereomodels for Divergent Reaction Pathways



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favored for the *N*,*O*-metalated azomethine ylides of methyl glycine imine. The consequence of such a geometric difference in the enolates should result in the divergent reaction pathways to either *concerted* [3 + 2]-cycloaddition or conjugate addition products.

In summary, we have developed enantiodivergent approaches to *endo*-pyrrolidnes based on two distinctive reaction pathways. While the stereodivergent approaches using the same chiral source are just gathering momentum in the catalytic asymmetric reactions,[12] the implementation of such asymmetric strategies to multiple synthetic transformations has been challenging due to the nature of specific factors that effects the reversal of stereoselectivity. By utilizing the catalyst- and substrate-controlled reaction pathways of imino esters, it was possible for the first time to demonstrate the reversal of enantioselectivity. The extensions of reaction pathway-controlled stereodivergent approaches to other catalytic reactions are currently underway in our laboratory, and our results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. 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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■ REFERENCES

(1) For reviews, see: (a) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *19*, 3693. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(2) For recent reviews, see: (a) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (c) Jiang, H.; Jørgensen, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492.

(3) For recent reviews, see: (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (b) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

(4) (a) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795. (b) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078. (c) de Cózar, A.; Cossío, F. P. *Phys. Chem. Chem. Phys.* **2011**, *13*, 10858.

(5) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750; For a stereochemical reassignment, see: *J. Am. Chem. Soc.* **2012**, *134*, 16918.

(6) According to Cossío's pyrrolidine nomenclature,[4a] the notation *endo* signifies the "*syn*" relationship between the R^1 of imino ester and the electron-withdrawing group (EWG) of alkenes. Consequently, the *exo* implies the "*anti*" relationship between the R^1 and the EWG. The notation *endo*′ and *exo*′ indicates an "*anti*" relationship between the R^1 and the ester moiety in pyrrolidines.

(7) (a) Kim, H. Y.; Shih, H.-J.; Knabe, W. E.; Oh, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7420. (b) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682. (c) Kim, H. Y.; Kim, H.; Oh, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 4476. (d) Kim, H. Y.; Oh, K. *Org. Lett.* **2011**, *13*, 1306.

(8) While 10 mol % of BD−$Cu(NTf_2)_2$ could be employed, the observed enantio- and diastereoselectivities were somewhat sensitive to the nature of substrates (i.e., **3d**, 95% yield, 7:1 dr, 76% ee).

(9) The opposite enantioselectivity was confirmed by converting *endo*-**7a** to *endo*-**3a** and comparing it with products from the concerted reaction pathway in Scheme 2.

(10) For *endo*-pyrrolidines with low ee's and dr's, see: (a) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979. (b) Li, Q.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2010**, *12*, 1080. (c) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7895. (d) Li, Q.; Ding, C.-H.; Li, X.-H.; Weissensteiner, W.; Hou, X.-L. *Synthesis* **2012**, *44*, 265. (e) Imae, K.; Konno, T.; Ogata, K.; Fukuzawa, S.-I. *Org. Lett.* **2012**, *14*, 4410. (f) Gonzalez-Esguevillas, M.; Adrio, J.; Carretero, J. C. *Chem. Commun.* **2012**, *48*, 2149. (g) Conde, E.; Bello, D.; de Cozar, A.; Sánchez, M.; Vázquez, M. A.; Cossío, F. P. *Chem. Sci.* **2012**, *3*, 1486. (h) Castello, L. M.; Nájera, C.; Sansano, J. M.; Larranaga, O.; de Cozar, A.; Cossío, F. P. *Org. Lett.* **2013**, *15*, 2902. For a successful *endo*-pyrrolidine formation, possibly via a concerted reaction pathway, see: (i) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338.

(11) For a stereoselective enolate formation of *N*-protected glycinates using LDA, see: Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789.

(12) For recent reviews, see: (a) Bartok, M. *Chem. Rev.* **2010**, *110*, 1663. (b) Escorihuela, J.; Burguete, M. I.; Luis, S. V. *Chem. Soc. Rev.* **2013**, *42*, 5595.

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