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A heterotrimetallic Pd–Sm–Pd complex for asymmetric Friedel–Crafts alkylations of pyrroles with nitroalkenes†

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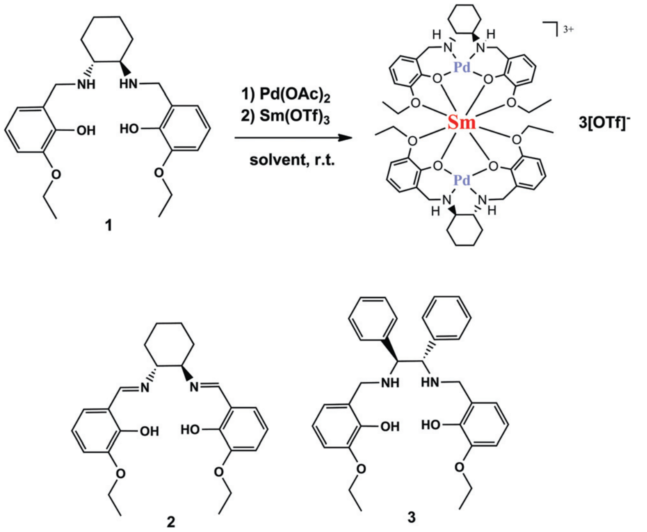
Catalytic asymmetric Friedel–Crafts alkylations of pyrroles and nitroalkenes were carried out by using a novel heterotrimetallic Pd–Sm–Pd catalyst based on a simple chiral ligand 1, to give the adducts with high yields and up to 93% ee.

In synthetic chemistry, the Friedel–Crafts alkylation is one of the most important C–C bond formation reactions.[1] Studies on catalytic asymmetric Friedel–Crafts reactions are a focus of current research, and great progress has been witnessed in the recent decade.[2,3] Pyrroles are important structural units or building blocks of natural products and pharmaceuticals.[4] However, the asymmetric Friedel–Crafts alkylations using pyrroles, especially unprotected pyrroles are less explored,[5] due to the relative instability of pyrroles towards acidic environments.[6] The asymmetric Friedel–Crafts reactions between pyrroles and nitroalkenes are very useful and highly desirable in organic synthesis. Surprisingly, efficient catalytic versions for these reactions remain extremely rare.[6,7] Among these, there are three examples concerning mono- or dinuclear zinc complexes,[6,7a,b] one of a Schiff base-Cu complex[7c] and an organocatalytic version dealing with chiral phosphoric acids as catalysts.[7d] Constable and coworkers have recently reported on the catalytic asymmetric Henry reaction using bimetallic complexes of salen or reduced salen ligands **1–3** (Scheme 1), and have found that both yields and enantioselectivities could be improved significantly in the presence of a second metal center.[8] We report here the asymmetric Friedel–Crafts alkylations of unprotected pyrroles with nitroolefins catalyzed by a novel heterotrinuclear Pd–Sm–Pd complex of **1**.

Salen-type Schiff base ligands with a pendant O_4 cavity have been extensively applied as bimetallic catalysts for a range of asymmetric reactions by Shibasaki and coworkers.[9] It has been recently observed that Schiff base **2** could be an ideal building block for construction of ionic di- or tri-metallic complexes.[10] Therefore, it was of interest to investigate the multimetallic systems involving ligands **1–3** as catalysts for asymmetric Friedel–Crafts alkylation of pyrrole **4a** with nitrostyrene **5a** (Table 2). The initial catalyst screening was performed in THF at room temperature using the combination of reduced Schiff base **1**, $Cu(OAc)_2$ and $Eu(OTf)_3$ in a 2 : 2 : 1 ratio (entry 1, Table 1).† To our delight, good enantioselectivity was observed for the product **6aa** (70% ee) with the presence of only 2.5 mol% of catalyst, while the yield was moderate. The ee was slightly increased by replacing $Eu(OTf)_3$ with $Sm(OTf)_3$, with almost no change in yield (entry 2, Table 1). However, the replacement of other rare earth salts gave much inferior results (entries 3 and 4, Table 1). Next changing the transition metals into Ni^{II}, Zn^{II}, Mn^{II} or Pd^{II} which are well suited for the inner N_2O_2 cavity of **1** was studied (entries 5–8, Table 1).[10] Interestingly, the choice of $Pd(OAc)_2$ resulted in a remarkable improvement in terms of yield and ee value (86% yield and 85% ee). Further trials in other solvent conditions gave much lower enantioselectivity, although the yield was very high using toluene as a solvent (entries 9–11, Table 1). It was assumed that a cooperative trimetallic complex species was responsible for the reactivity observed above, on the basis of our further catalysts screening, as no reaction happened at all while using $Pd(OAc)_2$ or $Sm(OTf)_3$ alone as



Scheme 1 Structures of chiral ligands **1–3** and proposed structure of ionic heterotrimetallic Pd–Sm–Pd complex.

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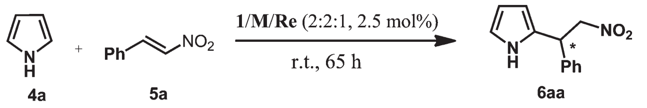
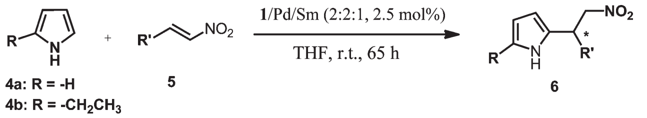
Table 1 Optimization of reaction conditions of heterotrimetallic complexes catalyzed Friedel–Crafts reaction of pyrrole and β-nitrostyrene[a]



Entry	Metal sources M[b]	Re[c]	Solvent	Yield (%)[d]	ee (%)[e]
1	Cu(II)	Eu	THF	52	70
2	Cu(II)	Sm	THF	54	72
3	Cu(II)	La	THF	40	34
4	Cu(II)	Yb	THF	0	—
5	Ni(II)	Sm	THF	0	—
6	Zn(II)	Sm	THF	14	12
7	Mn(II)	Sm	THF	<5	—
8	Pd(II)	Sm	THF	86	85
9	Pd(II)	Sm	EtOH	62	8
10	Pd(II)	Sm	CH_2Cl_2	92	60
11	Pd(II)	Sm	Toluene	95	67
12	Pd(II)	—	THF	0	—
13	—	Sm	THF	0	—
14[f]	Pd(II)	Sm	THF	38	85
15[g]	Pd(II)	Sm	THF	88	83
16[h]	Pd(II)	Sm	THF	71	19
17[i]	Pd(II)	Sm	THF	50	14
18[j]	Pd(II)	Sm	THF	<5	—

[a] Reactions performed with pyrrole **4a** (3 equiv.) and nitrostyrene **5a** (1 equiv.) in the air. [b] $M(OAc)_2$ was used. [c] $Re(OTf)_3$ was used, where Re represents rare earth. [d] Yields of isolated **6aa** by column chromatography. [e] Enantiomeric excess (ee) was determined by HPLC using a Chiralcel OD-H column. [f] The reaction was performed at 0 °C. [g] With 5 mol% catalyst. [h] **1**/**M**/**Re** = 1 : 1 : 1 and with 5 mol% catalyst. [i] Ligand **2** was used. [j] Ligand **3** was used.

Table 2 Catalytic asymmetric Friedel–Crafts reaction of various pyrroles and nitroalkenes[a]



Entry	Pyrrole	Nitroalkene (R′)	Product	Yield (%)[b]	ee (%)[c]
1	**4a**	C_6H_5– (**5a**)	**6aa**	86	85
2	**4a**	4-F–C_6H_5– (**5b**)	**6ab**	92	91
3	**4a**	4-Cl–C_6H_5– (**5c**)	**6ac**	94	71
4	**4a**	4-Br–C_6H_5– (**5d**)	**6ad**	93	80
5	**4a**	4-MeO–C_6H_5– (**5e**)	**6ae**	92	89
6	**4a**	2-Furyl– (**5f**)	**6af**	95	85
7	**4a**	2-Thiophenyl– (**5g**)	**6ag**	86	93
8	**4a**	*n*-Butyl– (**5h**)	**6ah**	55	59
9	**4b**	C_6H_5– (**5a**)	**6ba**	86	66
10	**4b**	4-Br–C_6H_5– (**5d**)	**6bd**	90	50
11	**4b**	2-Furyl– (**5f**)	**6bf**	92	85
12	**4b**	2-Thiophenyl– (**5g**)	**6bg**	94	87

[a] The reactions were performed using 2.5 mol% **1**–$Pd(OAc)_2$–$Sm(OTf)_3$ (2 : 2 : 1). [b] Yields of isolated **6** by column chromatography. [c] Enantiomeric excess (ee) was determined by HPLC using Chiralcel OD-H or AD-H columns.

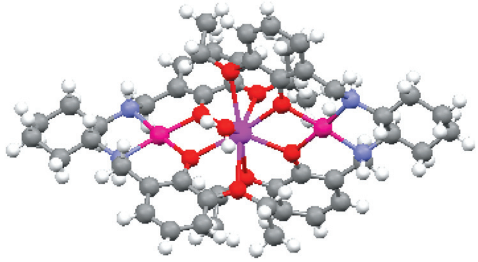


Fig. 1 X-ray structure of the cationic heterotrimetallic Pd–Sm–Pd complex with **1**. Three triflate counterions and solvent molecules were omitted for clarity.

metal salts (entries 12 and 13, Table 1). Lowering the reaction temperature, increasing the catalyst loading or changing the ratio of **1**, $Pd(OAc)_2$ and $Sm(OTf)_3$ did not improve the result significantly (entries 14–16, Table 1). The use of ligands **2** and **3** resulted in much lower ee value or even no reactivity (entries 17 and 18, Table 1). These results indicated that the **1**/$Pd(OAc)_2$/$Sm(OTf)_3$ (2 : 2 : 1) combination as well as THF as a solvent were essential to obtain both high reactivity and enantioselectivity in the present reaction.

The substrate scope of the reaction under optimized reaction conditions was investigated as summarized in Table 2. Several substituted nitroalkenes **5b–e**, containing both electron-donating and electron-withdrawing groups were tested, and excellent yields and high enantioselectivities were observed for the resulting adducts with **4a** (entries 2–5, Table 2). Heteroaryl-substituted nitroalkenes **5f** and **5g** were well tolerated for the reaction under the optimized conditions, and the thiophene-derived substrate gave the highest ee value (93% ee, entry 7, Table 2). In contrast, the alkyl-substituted nitroalkene **5h** gave much lower yield and selectivity (entry 8, Table 2). Substituted pyrroles were also tested. The pyrrole bearing an ethyl substituent at the 2-position was applicable for the Friedel–Crafts reactions (entries 9–12, Table 2), although in some cases only inferior enantioselectivities were obtained (entries 9 and 10, Table 2). Nevertheless, the observed catalyst system is suitable for a wide range of substrates for both substituted pyrroles and nitroalkenes as presented above, and the results here are well comparable to other reported results.[6,7]

The absolute stereochemistry of the products was determined by comparison of the optical rotations with those reported by You and Du *et al.* in the literature.[7] The absolute configuration of the products was determined to be *R*.

To ascertain the structure of the catalytic species in the reactions, **1**, $Pd(OAc)_2$ and $Sm(OTf)_3$ were combined in a 2 : 2 : 1 ratio in THF, after stirring and removal of the solvent, the resulting solid was recrystallized by slow diffusion of diethyl ether into a chloroform–toluene solution of **1a**, yellow crystals were obtained within two weeks (see ESI†). The main structure of the complex was unambiguously elucidated by single crystal X-ray crystallography, though the crystal quality was not perfect. Indeed, a heterotrinuclear complex was observed in the crystal structure (see Fig. 1 and Fig. S1†), which is consistent with the optimized catalyst system utilized for the asymmetric Friedel–Crafts alkylation. The samarium ion was bound between two [Pd-**1**] coordination domains with the outer O_4 cavities and one water molecule saturated the nine-coordinate sphere of Sm^{III}. We proposed that during the catalytic reaction, this trinuclear complex behaved as a bifunctional catalyst to activate both substrates with Pd^{II} and Sm^{III} active sites,[11] similar to the reported working model with a dinuclear Zn^{II} catalyst.[6]

In summary, the enantioselective Friedel–Crafts reactions of unprotected pyrroles with nitroalkenes catalyzed by a novel Pd–Sm–Pd heterotrimetallic complex based on a simple reduced Schiff base ligand. The catalyst can be readily prepared *in situ* and was structurally characterized by X-ray crystallography, and the reactions were usually performed under mild reaction conditions without protection. This protocol provides a facile access to highly enantioenriched 2-substituted and 2,5-disubstituted pyrroles. Further investigations concerning other applications of similar trimetallic complexes are under way.

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Notes and references

1 For reviews of Friedel–Crafts alkylation reactions, see: (*a*) G. A. Olah, *Friedel–Crafts and Related Reactions*, Wiley-Interscience, New York, 1964, vol. II, Part 1; (*b*) R. M. Roberts and A. A. Khalaf, *Friedel–Crafts Alkylation Chemistry A Century of Discovery*; Dekker, New York, 1984; (*c*) G. A. Olah, R. Krishnamurit, G. K. S. Prakash, *Friedel–Crafts Alkylations in Comprehensive Organic Synthesis*; Pergamon Press, Oxford, 1991.

2 For recent reviews, see: (*a*) M. Bandini, E. Emer, S. Tommasi and A. Umani-Ronchi, *Eur. J. Org. Chem.*, 2006, 3527; (*b*) M. Bandini, A. Melloni, S. Tommasi and A. Umani-Ronchi, *Synlett*, 2005, 1199–1222; (*c*) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 550–556; (*d*) K. A. E. Jørgensen, *Synthesis*, 2003, 1117.

3 For recent examples, see: (*a*) Y. X. Jia, S. F. Zhu, Y. Yang and Q. L. Zhou, *J. Org. Chem.*, 2006, **71**, 75; (*b*) H. M. Li, Y. Q. Wang and L. Deng, *Org. Lett.*, 2006, **8**, 4063; (*c*) R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576; (*d*) T. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903; (*e*) S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190.

4 For selected examples: (*a*) A. Fürstner, K. Radkowski and H. Peters, *Angew. Chem., Int. Ed.*, 2005, **44**, 2777; (*b*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (*c*) J. A. Johnson, L. Ning and D. Sames, *J. Am. Chem. Soc.*, 2002, **124**, 6900; (*d*) H. Hoffmann and T. Lindel, *Synthesis*, 2003, 1753; (*e*) G. Balme, *Angew. Chem., Int. Ed.*, 2004, **43**, 6238; (*f*) P. S. Baran, J. M. Richter and D. W. Lin, *Angew. Chem., Int. Ed.*, 2005, **44**, 609.

5 (*a*) G. Blay, I. Fernández, J. R. Pedro and C. Vila, *Org. Lett.*, 2007, **9**, 2601; (*b*) D. A. Evans, K. R. Fandrick, H. J. Song, K. A. Scheidt and R. S. Xu, *J. Am. Chem. Soc.*, 2007, **129**, 10029; (*c*) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcia and A. Linden, *J. Am. Chem. Soc.*, 2005, **127**, 4154; (*d*) W. Zhuang, N. Gathergood, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2001, **66**, 1009; (*e*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370; (*f*) B. F. Bonini, E. Capito, M. C. Franchini, M. Fochi, A. Ricci and B. Zwanenburg, *Tetrahedron: Asymmetry*, 2006, **17**, 3135; (*g*) G.-L. Li, G. B. Rowland, E. B. Rowland and J. C. Antilla, *Org. Lett.*, 2007, **9**, 4065; (*h*) S. Nakamura, Y. Sakurai, H. Nakashima, N. Shibata and T. Toru, *Synlett*, 2009, 1639; (*i*) L. Hong, C. Liu, W. Sun, L. Wang, K. Wong and R. Wang, *Org. Lett.*, 2009, **11**, 2177.

6 B. M. Trost and C. Müller, *J. Am. Chem. Soc.*, 2008, **130**, 2438.

7 (*a*) H. Liu, S.-F. Lu, J.-X. Xu and D.-M. Du, *Chem.–Asian J.*, 2008, **3**, 1111; (*b*) N. Yokoyama and T. Arai, *Chem. Commun.*, 2009, 3285; (*c*) F. Guo, D. Chang, G. Lai, T. Zhu, S. Xiong, S. Wang and Z. Wang, *Chem.–Eur. J.*, 2011, **17**, 11127; (*d*) Y.-F. Sheng, Q. Gu, A.-J. Zhang and S.-L. You, *J. Org. Chem.*, 2009, **74**, 6899.

8 (*a*) E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger, S. Schaffner and W.-D. Woggon, *New J. Chem.*, 2009, **33**, 1064; (*b*) E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger, S. Schaffner, W.-D. Woggon and J. A. Zampese, *New J. Chem.*, 2009, **33**, 2166.

9 (*a*) Z. Chen, H. Morimoto, S. Matsunga and M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 2170; (*b*) Z. Chen, K. Yakura, S. Matsunga and M. Shibasaki, *Org. Lett.*, 2008, **10**, 3239; (*c*) S. Handa, V. Gnanadesikan, S. Matsunga and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 4900; (*d*) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 3666; (*e*) S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 4925; (*f*) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 16438.

10 (*a*) E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger and J. A. Zampese, *CrystEngComm*, 2010, **12**, 1764 and references therein; (*b*) E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger and J. A. Zampese, *Inorg. Chim. Acta*, 2010, **363**, 4207.

11 We assumed that water molecule bound to the Sm^{III} center was readily removed in the presence of relatively strong coordinated substrates (bearing pyrrole–NH or nitro–O), thus the Sm^{III} ion of the complex activated one substrate and the Pd^{II} ion activated the other one.