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Combinatorial Synthesis and Evaluation of α-Iminocarboxamide-Nickel(II) Catalysts for the Copolymerization of Ethylene and a Polar Monomer

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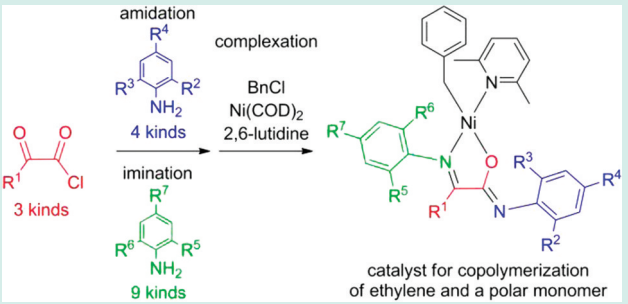
Supporting Information

ABSTRACT: Late-transition metal catalysts used for olefin polymerization, the so-called postmetallocenes, which includes α-iminocarboxamide-nickel(II) catalysts have attracted a great deal of attention because of many valuable features such as the copolymerization of α-olefins with polar monomers. In this paper, the combinatorial synthesis and evaluation of α-iminocarboxamide-nickel(II) catalysts are discussed for their roles in the discovery of a highly active catalyst and elucidation of its structure−activity relationship. The combinatorial optimization of each reaction condition was performed, then a combinatorial library of α-iminocarboxamides with systematically modified substituents was constructed by amidation of α-keto acid chlorides and subsequent imination of α-keto carboxamides in parallel fashion. As a result, 87 analytically pure α-iminocarboxamide ligands were successfully synthesized. α-Iminocarboxamide-nickel(II) catalysts were prepared from the synthesized α-iminocarboxamide ligands. The catalysts' activities for polymerization of ethylene and copolymerization of ethylene and 5-norbornen-2-ol were evaluated. Results of the present study revealed 9 novel active catalysts for ethylene polymerization and 7 novel active catalysts for copolymerization of ethylene and 5-norbornen-2-ol. It should be noted that the best catalysts for ethylene polymerization and for copolymerization in the present study showed higher activities compared to the known active catalyst. Polymerization activities of the catalysts varied dramatically according to the combination of substituents on the α-iminocarboxamides.



KEYWORDS: *olefin polymerization, α-iminocarboxamide-nickel(II) catalysts*

INTRODUCTION

Late-transition metal catalysts for olefin polymerization, the so-called postmetallocenes, have attracted a great deal of attention in both academia and industry, because these catalysts have many unique and practical features such as the copolymerization of α-olefins with certain comonomers possessing polar functionalities, chain-walking reactions to give hyper-branched polyolefins, and polymerization in polar solvents such as water.[1,2]

In 2001, Bazan, et al. disclosed α-iminocarboxamide-nickel(II) catalyst **1** for ethylene polymerization (Figure 1).[3] Upon activation with bis(1,5-cyclooctadiene)nickel (Ni(COD)$_2$), the catalysts promoted quasi-living copolymerization of ethylene and functionalized norbornenes to generate a variety of polyethylene-based materials, such as random copolymers,[4,5] block copolymers,[6−8] and polyolefins grafted with polar chains.[9,10]

The steric and electric effects of the substituents on the α-iminocarboxamide ligands were investigated by independently changing substituents R and R′.[4,11] It was reported that the binding mode of the catalysts is altered according to the substituent R′. As the bulk of the substituent R′ increases, the *N*,*O*-binding mode tends to prevail (Figure 1). However, reduction of the steric bulk gives rise to complexes that take advantage of the electronically preferred *N*,*N*-binding mode (Figure 1).[4] It is known that ethylene polymerization upon activation of Ni(COD)$_2$, is observed only with the *N*,*O*-bound species. As the bulk of the substituent R increases, monomer consumption activity increases. When R is an electron withdrawing group, the catalyst becomes more active.[11]

Although the structure−activity information described above is available and much progress has been made in theoretical calculations,[12−14] it remains difficult to estimate the copolymerization activity of the catalysts based on their structures. It seems to be difficult to optimize each substituent as an independent factor for the activity, because a change in one substituent influences the steric and electric environment of the other substituents.

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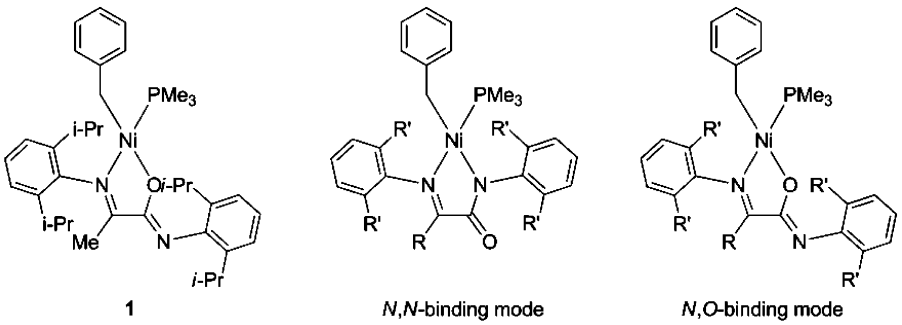


Figure 1. Structure of α-iminocarboxamide-nickel(II) catalyst **1**.

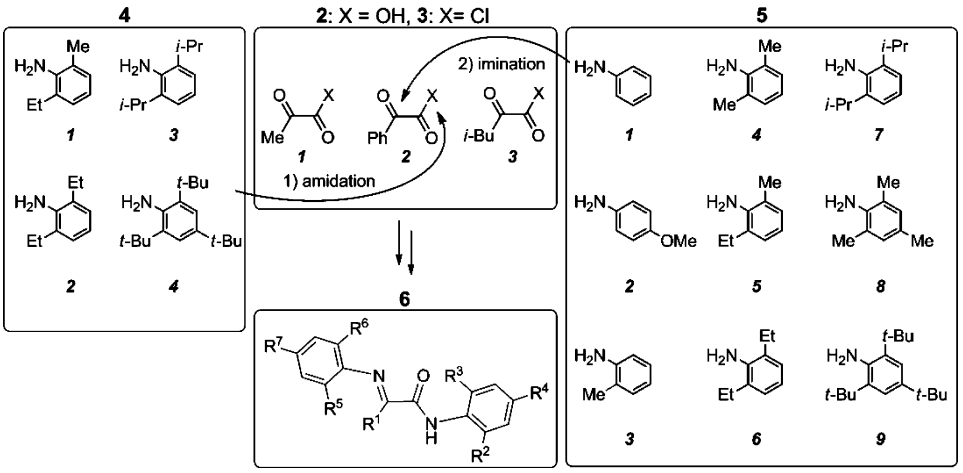
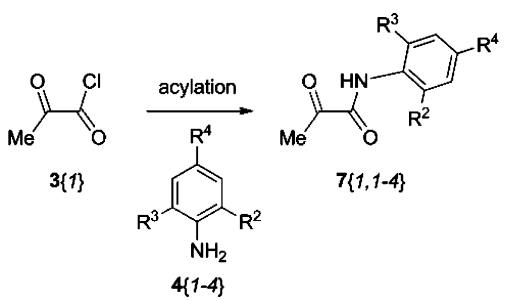


Figure 2. Combinatorial synthesis of α-imino carboxamides **6**.

Combinatorial chemistry, which revolutionized drug discovery, is very powerful when the rational design of molecules is difficult. We have reported the construction of combinatorial libraries based on biologically active natural products[15−36] and liquid crystals.[37−43] Combinatorial chemistry has recently become increasingly important in catalyst development as well.[44,45]

We anticipated that the best combination of substituents for copolymerization activity could be found, and the structure−activity relationship could be elucidated by constructing a combinatorial library consisting of α-iminocarboxamides with systematically modified substituents R and R′. Independent optimization of each substituent without changing the other substituents has been reported.[4,11] However, combinatorial optimization of substituents has not been reported. This paper is the first report of the construction of a combinatorial library of α-iminocarboxamides and the evaluation of the ethylene polymerization and copolymerization activities of α-iminocarboxamide-nickel(II) catalysts prepared from synthesized α-iminocarboxamides.

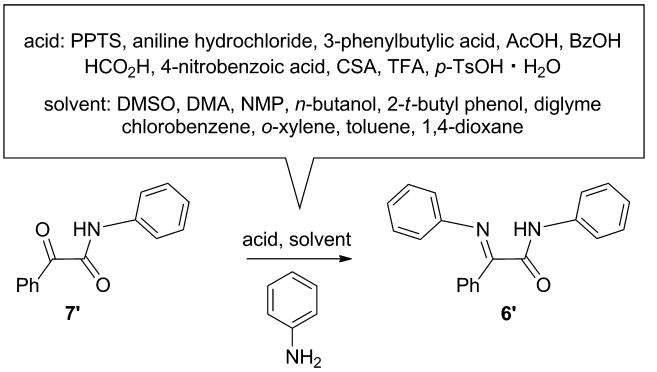
Scheme 1. Synthesis of α-Ketocarboxamide 7{*1,1−4*}



RESULTS AND DISCUSSION

The synthetic plan for the construction of a library of α-iminocarboxamides is shown in Figure 2. The aim was to synthesize 12 α-ketocarboxamides by the amidation of α-ketoacidchlorides **3**{*1−3*}, which can be easily derived from corresponding α-ketoacids **2**{*1−3*}, with substituted anilines **4**{*1−4*}. The desired α-iminocarboxamides **6**{*1−3,1−4,1−9*} were obtained by imination of the 12 α-ketocarboxamides with substituted anilines **5**{*1−9*}. This synthetic route consists of simple and reliable reactions, amidation and imination, and requires no special equipment such as a glovebox.[11]

Scheme 2. Combinatorial Optimization of Acid-Promoted Imination Reaction



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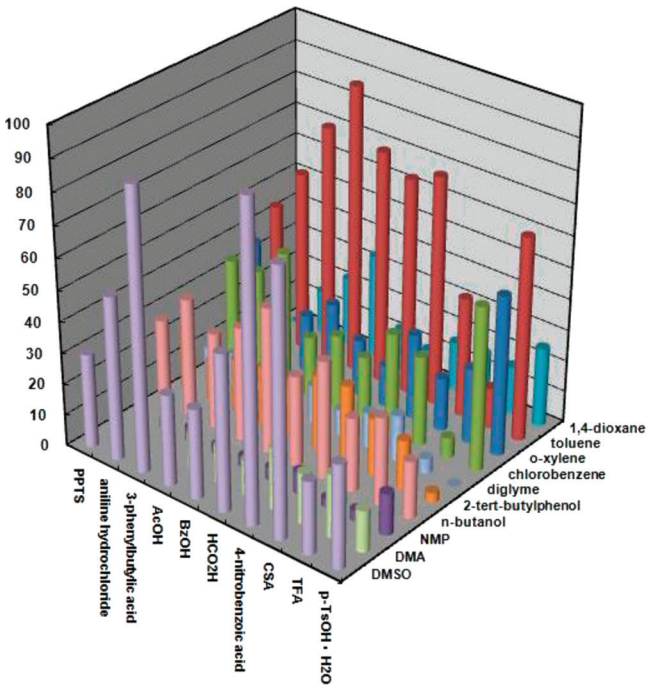

Figure 3. Combinatorial optimization of acid-promoted imination reaction.

Initially, we optimized the amidation conditions using α-ketoacidchloride **3**{*1*} and the substituted anilines **4**{*1*−*4*} (Scheme 1).[46] The α-ketoacidchloride **3**{*1*} was easily prepared from the corresponding α-ketoacid **2**{*1*} using α,α-dichloromethy methyl ether.[47] The optimized combination of base and solvent varied according to the substituents in the anilines. For example, the combination of Et_3N and toluene was suitable in the case of **4**{*1*−*3*}, whereas the combination of pyridine and CH_2Cl_2 was suitable in the case of **4**{*4*}.[46]

The pK_a of the protonic acids varies among solvents; therefore, the combinatorial optimization of protonic acids and solvents in an acid-mediated imination of α-ketocarboxamide **7′** with aniline was performed (Scheme 2). For this process, 10 acids and 10 solvents were examined for a total of 100 conditions. It is well-known that the rate of the imination reaction is highest around pK_a 4. Therefore, 8 weak acids including PPTS, aniline hydrochloride, 3-phenyl butylic acid, AcOH, BzOH, HCO_2H, 4-nitrobenzoic acid, and CSA were selected as candidates. Two strong acids, frequently used in imination reactions, TFA and *p*-TsOH·H_2O were also examined. Various solvents with different polarities were examined.

The mixtures of α-ketocarboxamide **7′**, aniline and acid in a solvent were stirred at 100 °C for 10 h utilizing a parallel synthesizer, Zodiac.[48] The obtained reaction mixtures were analyzed by LCUV/MS and the amount of the desired product was calculated by comparison of the product's UV intensity to that of an internal standard. The scores of all reaction conditions are shown in Figure 3 and Table 1. The best result was obtained from the combination of 4-nitrobenzoic acid and DMSO, and the observed relative UV intensity of the desired

Table 2. Acylation of Anilines 4{*1*−*4*} with α-Ketoacidchloride 3{*1*−*3*}

entry	products	yield[a]	entry	products	yield[a]	entry	products	yield[b]
1	7{*1,1*}	quant.	5	7{*2,1*}	quant.	9	7{*3,1*}	98%
2	7{*1,2*}	quant.	6	7{*2,2*}	94%	10	7{*3,2*}	quant.
3	7{*1,3*}	91%	7	7{*2,3*}	quant.	11	7{*3,3*}	88%
4	7{*1,4*}	89%	8	7{*2,4*}	quant.	12	7{*3,4*}	94%

[a]Isolated yield. [b]Isolated yield in 2 steps from **2**{*3*}

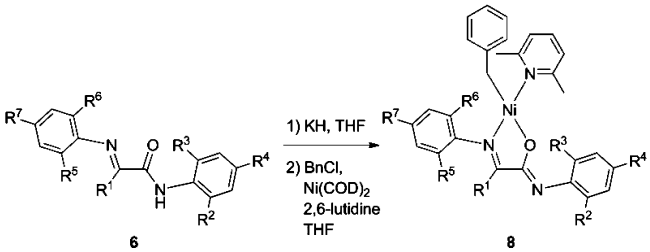

Figure 4. Preparation of α-iminocarboxamide-nickel(II) catalysts **8** from α-imino carboxamides **6**.

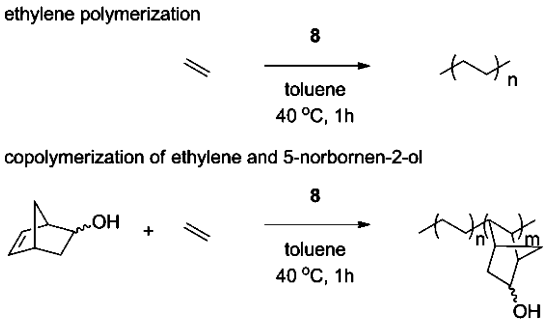

Figure 5. Ethylene polymerization and copolymerization of ethylene and 5-norbornen-2-ol.

Table 1. Combinatorial Optimization of Acid-Promoted Imination Reaction[a]

	dioxane	toluene	*o*-xylene	chloro benzene	diglyme	2-*t*-butyl phenol	*n*-butanol	NMP	DMA	DMSO
PPTS	0	44	36	34	9	19	27	3	18	30
aniline hydrochloride	14	58	22	34	11	13	38	3	12	52
3-phenyl butylic acid	22	76	19	44	5	18	31	4	13	90
AcOH	33	92	26	20	10	19	37	3	11	29
BzOH	12	75	18	24	12	20	47	3	12	29
HCO_2H	9	69	13	21	8	24	29	4	12	50
4-nitro benzoic acid	16	74	27	32	11	25	38	7	20	100
CSA	16	38	17	29	15	19	24	3	16	84
TFA	16	13	24	6	5	16	28	3	20	23
p-TsOH·H_2O	25	65	51	52	0	3	18	13	13	33

[a]The observed relative UV intensity of the desired product by the best combination of 4-nitrobenzoic acid and DMSO was assigned a score of 100. The relative UV intensities of the desired product obtained from other reaction conditions were assigned scores from 0 to 100.

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Table 3. Construction of a Combinatorial Library of α-Iminocarboxamides 6

entry	products	yield[a] (%)	entry	products	yield[a] (%)	entry	products	yield[a] (%)
1	6{1,1,1}	35	37	6{2,1,1}	30	73	6{3,1,1}	18
2	6{1,1,2}	87	38	6{2,1,2}	82	74	6{3,1,2}	33
3	6{1,1,3}	37	39	6{2,1,3}	60	75	6{3,1,3}	21
4	6{1,1,4}	24	40	6{2,1,4}	57	76	6{3,1,4}	10
5	6{1,1,5}	17	41	6{2,1,5}	23	77	6{3,1,5}	28
6	6{1,1,6}	45	42	6{2,1,6}	9	78	6{3,1,6}	9
7	6{1,1,7}	45	43	6{2,1,7}	48	79	6{3,1,7}	3
8	6{1,1,8}	23	44	6{2,1,8}	5	80	6{3,1,8}	12
9	6{1,1,9}	18	45	6{2,1,9}	b	81	6{3,1,9}	b
10	6{1,2,1}	55	46	6{2,2,1}	88	82	6{3,2,1}	18
11	6{1,2,2}	92	47	6{2,2,2}	20	83	6{3,2,2}	29
12	6{1,2,3}	54	48	6{2,2,3}	32	84	6{3,2,3}	18
13	6{1,2,4}	27	49	6{2,2,4}	62	85	6{3,2,4}	8
14	6{1,2,5}	85	50	6{2,2,5}	37	86	6{3,2,5}	14
15	6{1,2,6}	31	51	6{2,2,6}	42	87	6{3,2,6}	12
16	6{1,2,7}	65	52	6{2,2,7}	11	88	6{3,2,7}	14
17	6{1,2,8}	69	53	6{2,2,8}	73	89	6{3,2,8}	26
18	6{1,2,9}	23	54	6{2,2,9}	b	90	6{3,2,9}	b
19	6{1,3,1}	53	55	6{2,3,1}	41	91	6{3,3,1}	21
20	6{1,3,2}	quant.	56	6{2,3,2}	38	92	6{3,3,2}	15
21	6{1,3,3}	20	57	6{2,3,3}	15	93	6{3,3,3}	23
22	6{1,3,4}	98	58	6{2,3,4}	7	94	6{3,3,4}	16
23	6{1,3,5}	47	59	6{2,3,5}	8	95	6{3,3,5}	45
24	6{1,3,6}	24	60	6{2,3,6}	69	96	6{3,3,6}	10
25	6{1,3,7}	78	61	6{2,3,7}	59	97	6{3,3,7}	12
26	6{1,3,8}	74	62	6{2,3,8}	quant.	98	6{3,3,8}	19
27	6{1,3,9}	b	63	6{2,3,9}	b	99	6{3,3,9}	b
28	6{1,4,1}	92	64	6{2,4,1}	9	100	6{3,4,1}	b
29	6{1,4,2}	77	65	6{2,4,2}	10	101	6{3,4,2}	12
30	6{1,4,3}	27	66	6{2,4,3}	34	102	6{3,4,3}	b
31	6{1,4,4}	37	67	6{2,4,4}	2	103	6{3,4,4}	b
32	6{1,4,5}	quant.	68	6{2,4,5}	b	104	6{3,4,5}	b
33	6{1,4,6}	53	69	6{2,4,6}	b	105	6{3,4,6}	b
34	6{1,4,7}	23	70	6{2,4,7}	b	106	6{3,4,7}	b
35	6{1,4,8}	12	71	6{2,4,8}	b	107	6{3,4,8}	b
36	6{1,4,9}	b	72	6{2,4,9}	b	108	6{3,4,9}	b

[a]Isolated yield. [b]Imination did not proceed.

product was assigned a score of 100. The relative UV intensities of the desired product obtained from other reaction conditions were then assigned scores from 0 to 100 (Figure 3 and Table 1). The combination of AcOH and toluene also afforded a result comparable to the best combination (score = 92). It is sometimes difficult to find the best combination by optimizing each factor (acid and solvent) independently. For example, if 10 solvents were examined using TFA, which is a frequently used acid in imination reactions, the optimal solvent was *n*-butanol (Table 1). All 10 acids were then examined in *n*-butanol solvent. The optimal acid was BzOH (Table 1). However, the combination of BzOH and *n*-butanol was not an optimal combination. Thus, combinatorial optimization of reaction conditions is a very powerful and reliable method. For convenience during the workup process, we employed the second-best combination, AcOH and toluene, for construction of the α-iminocarboxamide library.

The combinatorial library of α-iminocarboxamide was constructed by the procedure developed. α-Ketoacid chloride **3**{*2*} was easily prepared from the corresponding α-ketoacid **2**{*2*}, using the same reaction condition for the synthesis of **3**{*1*}. α-Ketoacid chloride **3**{*3*} was prepared by treating α-ketoacid **2**{*3*} with oxalyl chloride and NEt_3 in toluene, which was then used for the amidation reaction without further purification.[46] Twelve α-ketocarboxamides were prepared by amidation of the α-ketoacidchlorides **3**{*1*−*3*} with the substituted anilines **4**{*1*−*4*} (Table 2). For amidation with the anilines **4**{*1*−*3*}, the combination of NEt_3 and toluene was employed (entries 1−3, 5−7, and 9−11). On the other hand, for amidation with the aniline **4**{*4*}, the combination of pyridine and CH_2Cl_2 was employed (entries 4, 8, 12). All 12 α-ketocarboxamides were obtained in good to excellent yields.

Subsequent imination of the 12 α-ketocarboxamides with anilines **5**{*1*−*9*} was carried out using AcOH and toluene. In the case of R^1 = Me group, all the intended products were obtained (entries 1−36) except for **6**{*1,3,9*} and **6**{*1,4,9*} (Table 3 entries 27, 36) with a combined steric bulk of aryl substituents that was the largest. In the case of R^1 = Ph and *i*-Bu group, imination with the largest aniline **5**{*9*} did not proceed (Table 3 entries 45, 54, 63, 72, 81, 90, 99, and 108). In addition, imination of the bulky α-ketocarboxamides, **7**{*2,4*} and **7**{*3,4*} afforded unsatisfactory results (Table 3 entries 64−72, and 100−108). The combined steric bulk of substituents R^1−R^7 (Figure 2) largely influenced the results of imination.

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Table 4. Polymerization Activities of α-Iminocarboxamide-nickel(II) Catalysts 8{*1,1−4,1−9*}

entry	catalysts	activity[a]	activity[b]
1	8{*1,1,1*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0
2	8{*1,1,2*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	*c*
3	8{*1,1,3*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	0
4	8{*1,1,4*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	0	*c*
5	8{*1,1,5*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	0	*c*
6	8{*1,1,6*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	0	*c*
7	8{*1,1,7*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	21800	11900
8	8{*1,1,8*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	*c*
9	8{*1,1,9*} (R^1 = Me, R^2 = Et, R^3 = Me, R^4 = H, R^5 = *t*-Bu, R^6 = *t*-Bu, R^7 = *t*-Bu)	0	*c*
10	8{*1,2,1*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0
11	8{*1,2,2*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	0
12	8{*1,2,3*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	0
13	8{*1,2,4*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	2400	0
14	8{*1,2,5*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	7300	0
15	8{*1,2,6*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	1600	1300
16	8{*1,2,7*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	25000	17300
17	8{*1,2,8*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	*c*
18	8{*1,2,9*} (R^1 = Me, R^2 = Et, R^3 = Et, R^4 = H, R^5 = *t*-Bu, R^6 = *t*-Bu, R^7 = *t*-Bu)	0	0
19	8{*1,3,1*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0
20	8{*1,3,2*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	0
21	8{*1,3,3*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	1300	0
22	8{*1,3,4*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	5300	0
23	8{*1,3,5*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	6700	0
24	8{*1,3,6*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	0	0
25	8{*1,3,7*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	42000	15000
26	8{*1,3,8*} (R^1 = Me, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	6000	2700
27	8{*1,4,1*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = H, R^6 = H, R^7 =H)	3000	0
28	8{*1,4,2*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = H, R^6 = H, R^7 = OMe)	0	0
29	8{*1,4,3*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Me, R^6 = H, R^7 = H)	4600	0
30	8{*1,4,4*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Me, R^6 = Me, R^7 = H)	0	0
31	8{*1,4,5*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Et, R^6 = Me, R^7 = H)	19400	5000
32	8{*1,4,6*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Et, R^6 = Et, R^7 = H)	2500	0
33	8{*1,4,7*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	12900	5900
34	8{*1,4,8*} (R^1 = Me, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Me, R^6 = Me, R^7 = Me)	0	0

[a]Reactivity of catalysts **8** in the homopolymerization of ethylene (g-polymer/mol-**6**/h). [b]Reactivity of catalysts **8** in the copolymerization of ethylene with 5-norbornen-2-ol (g-polymer/mol-**6**/h). [c]Reactivity of catalysts **8** was not evaluated because ethylene polymerization activity of the catalysts was very low.

Synthesized α-iminocarboxamides were purified by silica gel column chromatography, and 87 analytically pure products were obtained from 108 trials. The structures of those products were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and HRMS.

α-Iminocarboxamide-nickel(II) catalysts **8** were prepared from synthesized α-iminocarboxamides **6** according to a previously reported procedure,[49] after some modifications (Figure 4). The α-iminocarboxamide was deprotonated with an excess amount of KH and treated with a mixture of Ni(COD)$_2$, BnCl and 2,6-lutidine in THF. The resulting solution was concentrated in vacuo, and diluted with benzene. Insoluble salts were removed by filtration to give a crude solution of α-iminocarboxamide-nickel(II) catalysts **8**. The crude solutions were used for the evaluation of polymerization activities of alkenes, without further purification for the sake of throughput improvement.

Activities of the prepared catalysts **8** for ethylene polymerization and copolymerization of ethylene and 5-norbornen-2-ol were evaluated (Tables 4−6) by using the Endeavor Catalyst Screening System[50] based on Bazan's procedure.[49] Ethylene homopolymerization was initiated by introducing ethylene gas (7.0 bar) to a solution of **8** (10 μmol) in C_6D_6 (1 mL) and dry toluene (4 mL) at 40 °C. Copolymerization of ethylene and 5-norbornen-2-ol was carried out in the same manner, except that 5-norbornen-2-ol (375 μmol) was added to the catalyst solution prior to heating and ethylene introduction. Polymerization activity (shown in g-polymer/mol-**6**/hour) was determined based on the amount of ethylene consumption and the resulting polymer weight.

In the present study, 9 novel active catalysts, 8{*1,1,7*}, 8{*1,2,7*}, 8{*1,4,5*}, 8{*1,4,7*}, 8{*2,3,6*}, 8{*2,3,7*}, 8{*3,1,6*}, 8{*3,3,6*}, and 8{*3,3,7*}[51] (Tables 4−6, entries 7, 16, 31, 33, 56, 57, 68, 84, and 85) showed high activity for ethylene polymerization (>10000 g-polymer/mol-**6**/h). The high-throughput evaluation method used in the present study proved to be reliable, as an active catalyst, 8{*1,3,7*}[49] (Table 4, entry 25), also showed high ethylene polymerization activity. It should be noted that the activities of catalysts 8{*2,3,7*}, and 8{*3,3,7*} were higher than that of known active catalyst 8{*1,3,7*}. The catalysts that had bulky substituents R^2−R^7 on their α-iminocarboxamide ligands tended to have high ethylene polymerization activity. This observation is consistent with a previous report.[4] The Me and *i*-Bu groups were more suitable than the Ph group as an R^1 substituent for ethylene polymerization (Tables 4−6). The combination of R^2 = R^3 = R^5 = R^6 = *i*-Pr, R^4 = R^7 = H afforded the best results regardless of substitutent R^1 (Tables 4−6, entries 25, 57 and 85). It is interesting that the optimal substituents R^2−R^4 differed from substituents R^5−R^7. For instance, in the case of R^1 = Me group, the optimal combination of substituents R^2−R^4 was R^2 = R^3 = *i*-Pr, R^4 = H when the combination of substituents R^5−R^7 was R^5 = R^6 = Me, R^7 = H, or R^5 = R^6 = *i*-Pr, R^7 = H, or R^5 = R^6 = R^7 = Me (Table 4, entries 22, 25 and 26), whereas the optimal combination of substituents R^2−R^4 was R^2 = R^3 = R^4 = *t*-Bu

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Table 5. Polymerization Activities of α-Iminocarboxamide-nickel(II) Catalysts 8{*2,1−4,1−8*}

entry	catalysts	activity[a]	activity[b]	entry	catalysts	activity[a]	activity[b]
35	8{*2,1,1*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0	49	8{*2,2,7*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	0	0
36	8{*2,1,2*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	*c*	50	8{*2,2,8*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	*c*
37	8{*2,1,3*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	*c*	51	8{*2,3,1*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0
38	8{*2,1,4*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	0	0	52	8{*2,3,2*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	0
39	8{*2,1,5*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	0	0	53	8{*2,3,3*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	*c*
40	8{*2,1,6*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	0	0	54	8{*2,3,4*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	0	0
41	8{*2,1,7*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	0	*c*	55	8{*2,3,5*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	5700	0
42	8{*2,1,8*} (R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	0	56	8{*2,3,6*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	13000	3000
43	8{*2,2,1*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	*c*	57	8{*2,3,7*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	50900	7800
44	8{*2,2,2*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	0	58	8{*2,3,8*} (R^1 = Ph, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	0
45	8{*2,2,3*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	0	59	8{*2,4,1*} (R^1 = Ph, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = H, R^6 = H, R^7 =H)	0	0
46	8{*2,2,4*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	6100	0	60	8{*2,4,2*} (R^1 = Ph, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = H, R^6 = H, R^7 = OMe)	0	0
47	8{*2,2,5*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	0	0	61	8{*2,4,3*} (R^1 = Ph, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Me, R^6 = H, R^7 = H)	0	0
48	8{*2,2,6*} (R^1 = Ph, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	3000	0	62	8{*2,4,4*} (R^1 = Ph, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = Me, R^6 = Me, R^7 = H)	*d*	*d*

[a]Reactivity of catalysts **8** in homopolymerization of ethylene (g-polymer/mol-**6**/h). [b]Reactivity of catalysts **8** in copolymerization of ethylene with 5-norbornen-2-ol (g-polymer/mol-**6**/h). [c]Reactivity of catalysts **8** was not evaluated because ethylene polymerization activity of the catalysts was very low. [d]The amount of the prepared α-iminocarboxamide ligand **6**{*2,4,4*} was not enough to evaluate polymerization activity.

Table 6. Polymerization Activities of α-Iminocarboxamide-nickel(II) Catalysts 8{*3,1−4,1−8*}

entry	catalysts	activity[a]	activity[b]	entry	catalysts	activity[a]	activity[b]
63	8{*3,1,1*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0	76	8{*3,2,6*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	0	0
64	8{*3,1,2*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	*c*	77	8{*3,2,7*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	9600	1300
65	8{*3,1,3*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	0	78	8{*3,2,8*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	0
66	8{*3,1,4*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	2400	0	79	8{*3,3,1*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0
67	8{*3,1,5*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	0	0	80	8{*3,3,2*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	0
68	8{*3,1,6*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	23000	0	81	8{*3,3,3*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	0
69	8{*3,1,7*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	5400	0	82	8{*3,3,4*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	1900	0
70	8{*3,1,8*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Me, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	4200	0	83	8{*3,3,5*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	6800	0
71	8{*3,2,1*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = H, R^6 = H, R^7 =H)	0	0	84	8{*3,3,6*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Et, R^6 = Et, R^7 = H)	26900	6200
72	8{*3,2,2*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = H, R^6 = H, R^7 = OMe)	0	*c*	85	8{*3,3,7*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = *i*-Pr, R^6 = *i*-Pr, R^7 = H)	71800	11560
73	8{*3,2,3*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = H, R^7 = H)	0	0	86	8{*3,3,8*} (R^1 = *i*-Bu, R^2 = *i*-Pr, R^3 = *i*-Pr, R^4 = H, R^5 = Me, R^6 = Me, R^7 = Me)	0	0
74	8{*3,2,4*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Me, R^6 = Me, R^7 = H)	0	0	87	8{*3,4,2*} (R^1 = *i*-Bu, R^2 = *t*-Bu, R^3 = *t*-Bu, R^4 = *t*-Bu, R^5 = H, R^6 = H, R^7 = OMe)	0	*c*
75	8{*3,2,5*} (R^1 = *i*-Bu, R^2 = Et, R^3 = Et, R^4 = H, R^5 = Et, R^6 = Me, R^7 = H)	0	0				

[a]Reactivity of catalysts **8** in homopolymerization of ethylene (g-polymer/mol-**6**/h). [b]Reactivity of catalysts **8** in copolymerization of ethylene with 5-norbornen-2-ol (g-polymer/mol-**6**/h). [c]Reactivity of catalysts **8** was not evaluated because ethylene polymerization activity of the catalysts was very low.

when the combination of substituents R^5–R^7 was R^5 = R^6 = R^7 = H or R^5 = Me, R^6 = R^7 = H or R^5 = Et, R^6 = Me, R^7 = H or R^5 = R^6 = Et, R^7 = H (Table 4, entries 27, 29, 31 and 32). In the case of R^1 = *i*-Bu group, the optimal combination of

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substituents R^2–R^4 was R^2 = Et, R^3 = Me, R^4 = H when the combination of substituents R^5–R^7 was R^5 = R^6 = Me, R^7 = H, or R^5 = R^6 = R^7 = Me (Table 6, entries 66 and 70), whereas the optimal combination of substituents R^2–R^4 was R^2 = R^3 = *i*-Pr, R^4 = H when the combination of substituents R^5–R^7 was R^5 = Et, R^6 = Me, R^7 = H or R^5 = R^6 = Et, R^7 = H or R^5 = R^6 = *i*-Pr, R^7 = H (Table 6, entries 83–85).

Seven novel catalysts, **8**{*1,1,7*}, **8**{*1,2,7*}, **8**{*1,4,5*}, **8**{*1,4,7*}, **8**{*2,3,7*}, **8**{*3,3,6*}, and **8**{*3,3,7*} (Table 4–6, entries 7, 16, 31, 33, 57, 84, and 85), showed high activity for copolymerization of ethylene and 5-norbornen-2-ol (>5000 g-polymer/mol-**6**/h). A known active catalysts **8**{*1,3,7*}[49] (Table 4, entry 25), also showed high activity. It should be noted that the activity of catalyst **8**{*1,2,7*} was higher than that of the known active catalyst **8**{*1,3,7*}. Interestingly, the optimal combination of substituents R^2–R^7 differs from substitutent R^1. The combination of R^2 = R^3 = Et, R^4 = R^7 = H, R^5 = R^6 = *i*-Pr afforded the best result when R^1 = Me group (Table 4, entry 16), whereas the same combination of R^2–R^7 afforded the unsatisfactory results when R^1 = Ph or *i*-Bu group (Tables 5 and 6, entries 49 and 77). In the case of R^1 = Ph or *i*-Bu group, the combination of R^2 = R^3 = R^5 = R^6 = *i*-Pr, R^4 = R^7 = H afforded the best result (Tables 5 and 6, entries 57 and 85).

Overall, the novel catalyst **8**{*3,3,7*} showed the highest activity for ethylene polymerization. It is noteworthy, however, that it was not the best catalyst for copolymerization of ethylene and 5-norbornen-2-ol. The novel catalyst **8**{*1,2,7*} showed the highest activity for copolymerization. To identify the binding mode of catalyst **8**{*1,2,7*}, purification and NMR analysis was carried out. The observed NMR spectra was quite similar to the reported NMR spectra of a known similar catalyst **8**{*1,3,7*}.[49] Therefore, the novel catalyst **8**{*1,2,7*} is supposed to be *N,O*-binding catalyst.

CONCLUSION

The solution-phase combinatorial synthesis of α-iminocarboxamide ligands using an amidation/imination sequence was successfully demonstrated. In the amidation reaction, the combination of Et_3N and toluene was effective for the less bulky anilines, while the combination of pyridine and CH_2Cl_2 was suitable for the bulky anilines. Combinatorial optimization of the acid-mediated imination conditions disclosed that the best combinations were 4-nitrobenzoic acid and DMSO, and AcOH and toluene. A total of 87 analytically pure α-iminocarboxamides were obtained from 108 trials using the sequence developed. Activities of the α-iminocarboxamide-nickel(II) catalysts prepared from synthesized α-iminocarboxamides for polymerization of ethylene and copolymerization of ethylene and 5-norbornen-2-ol were evaluated. As a result, 9 novel active catalysts (>10000 g-polymer/mol-**6**/h) for ethylene polymerization and 7 novel active catalysts (>5000 g-polymer/mol-**6**/h) for copolymerization of ethylene and 5-norbornen-2-ol were identified. It should be noted that the activities of catalysts **8**{*3,3,7*} for ethylene polymerization and **8**{*1,2,7*} for copolymerization were higher than that of known active catalyst **8**{*1,3,7*}. Polymerization activities of catalysts varied dramatically according to their combination of substituents R^1–R^7 on the α-iminocarboxamides. The construction of a combinatorial library of ligands is, therefore, a very powerful tool for catalyst development.

ASSOCIATED CONTENT

Supporting Information

Analytical data (^1H, ^{13}C NMR and IR spectra) for the compounds are provided. This information is available free of charge via the Internet at http://pubs.acs.org/.

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