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Polymer-Supported Chiral Catalysts with Positive Support Effects

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Abstract—In this paper, we discuss the rational design of polymeric catalysts and the positive effect of polymer supports on the catalytic asymmetric reactions. The attachment of chiral catalysts to soluble polymers, particularly dendritic polymers, offered a potential combination of the advantages of homogeneous and heterogeneous asymmetric catalysis. © 2002 Elsevier Science Ltd. All rights reserved.

Homogeneous asymmetric catalysis is one of the most important developments in modern chemistry over the past several decades. Many chiral catalysts have been found to exhibit high activities and enantioselectivities.[1] Since most chiral catalysts are expensive, it is highly desirable to reuse the catalyst after each reaction. A common solution to this problem is to 'heterogenize' a homogeneous catalyst, either by anchoring the catalyst on a solid support or by using a liquid–liquid two-phase system.[2] However, the immobilized chiral catalysts often suffered from lowered catalytic activity and/or enantioselectivity. In the case of insoluble polymer-supported catalysts, for example, the catalytic sites are randomly oriented among the solid support and the microenvironments around the active sites are usually not clear. The lowered catalytic activity and enantioselectivity of this class of catalysts are thought to be due to the restriction of the insoluble polymer matrix. Therefore, the design of highly effective polymer-supported chiral catalyst with positive influence of the polymer support on the catalyst is highly desirable. For this purpose, we have developed several kinds of effective polymer-supported chiral catalysts by using insoluble polymer, soluble polymer, or dendrimer as catalyst supports.

Insoluble Polymer-Supported Catalyst[3]

Inspired by the idea of solid peptide synthesis developed by Merrifield in the early 1960s, the methodology of attaching chiral ligands onto cross-linked polymers has been widely applied to the development of new polymer-supported catalysts for asymmetric reactions. In a recent study, we developed an effective polymer-supported catalyst from 1,1′-Bi-2-naphthol (BINOL), which has been extensively studied as a chiral auxiliary in asymmetric synthesis.[4] An aminomethylated polystyrene resin was used to tether to BINOL at the 3-position or 3,3′-positions of the naphthyl-backbone to take advantage of its proximity to the chiral catalytic center, so as to better examine the effect of the polymer matrix on the catalyst. Two polymer-supported BINOLs, **1** and **2** (Fig. 1) were synthesized by coupling an aminomethyl polystyrene resin with (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3-carboylic acid and (*S*)-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboylic acid, respectively. Two small molecule model compounds, **3** and **4** (shown in Fig. 1) were also synthesized for the purpose of comparison. The resulting functionalized polymers and their small molecule analogues were tested as chiral ligands in the Ti-catalyzed enantioselective addition of diethylzinc to aldehydes. Interestingly in most cases the heterogeneous chiral ligands were found to be more effective than their homogeneous counterparts. The C_2-symmetric polymer ligand **2** with two polymer chains at the 3,3′-positions of BINOL gave much higher enantioselectivity than **1** with only one polymer chain in the

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asymmetric reaction of diethylzinc to aldehyde substrates (Tables 1 and 2). A comparison of the structures of the polymer-supported ligands **1** and **2**, respectively, with their homogeneous ligands **3** and **4** offered an explanation for the difference in their effectiveness as chiral ligands in the asymmetric reaction (Fig. 2). The higher conformational rigidity of polymer **2** gave better steric control, consequently resulted in significant improvement of enantioselectivity.

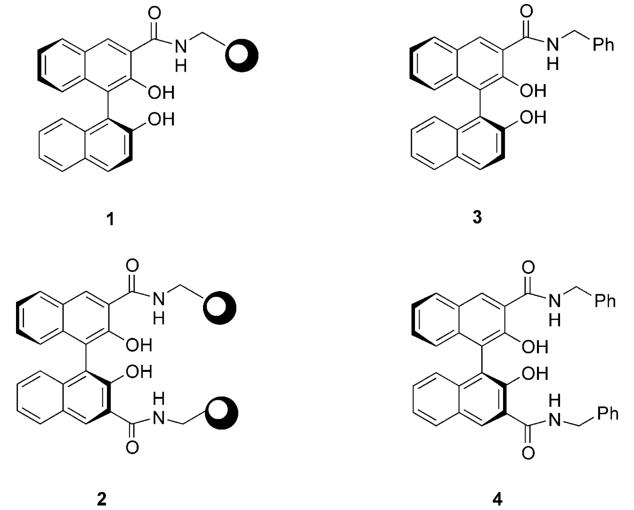


Figure 1.

Table 1. Asymmetric addition of Et_2Zn to aldehydes catalyzed by **1** and **3**

Run	R/RCHO	Temperature (°C), rt (h)		Yield (%)[a]		ee (%)[b]	
		1	**3**	**1**	**3**	**1**	**3**
1	Ph	0, 35	0, 20	88	92	65	61
2	4-ClPh	0, 35	0, 20	94	95	60	33
3	3-ClPh	0, 35	0, 20	91	95	55	64
4	4-MeOPh	0, 35	0, 20	88	85	51	28
5	3-MeOPh	0, 35	0, 20	82	92	61	55
6	2-MeOPh	0, 35	0, 20	91	93	34	3
7	4-NO_2Ph	0, 40	—	85	—	82	—
8	3-NO_2Ph	0, 50	0, 40	89	93	79	76
9	PhCH=CH	0, 35	0, 20	92	90	35	32
10	Piperonyl	0, 35	0, 20	88	95	41	67

[a]Isolated yields.
[b]Determined by HPLC with chiral OD column.

Table 2. Asymmetric addition of Et_2Zn to aldehydes catalyzed by **2** and **4**

Run	R/RCHO	Temperature (°C), rt (h)		Yield (%)[a]		ee (%)[b,c]		
		2	**4**	**2**	**4**	**2**	**4**	
1	Ph	0, 24	0, 15	93	93	97	63	(91.5)
2	2-ClPh	0, 25	—	92	—	91	—	(68.6)
3	3-ClPh	0, 24	0, 24	89	92	94	94	(88.2)
4	4-ClPh	0, 30	—	88	—	92	—	(88.1)
5	2-MeOPh	0, 24	—	92	—	89	—	
6	3-MeOPh	0, 28	—	78	—	92	—	(94.0)
7	4-MeOPh	0, 48	—	90	—	83	—	(79.0)
8	3-NO_2Ph	0, 54	—	88	—	99	—	(70.0)
9	4-NO_2Ph	0, 48	—	90	—	96	—	
10	4-N(Me)$_2$Ph	0, 18	—	97	—	57	—	
11	3,4-(MeO)$_2$Ph	0, 24	—	93	—	95	—	
12	Piperonyl	0, 30	0, 20	89	87	65	36	
13	1-Br-2-Nap	0, 28	—	95	—	95	—	
14	(E)PhCH=CH	0, 28	0, 20	97	89	93	36	
15	2-Nap	0, 48	—	89 —	94	—		
16	2-MeO-1-Nap	0, 24	—	87	—	99	—	

[a]Isolated yields.
[b]Determined by HPLC with chiral OD column.
[c]The data in brackets were the results from a study using BINOL ligand. See ref 5.

Soluble Polymer-Supported Catalyst[6]

Another approach to address the problem of catalyst separation and recycling is to use a soluble polymer support. A soluble polymer-supported catalyst behaves like a homogeneous catalyst during the reaction and can be easily separated via precipitation upon the completion of the reaction. This class of catalyst combines the advantages of homogeneous and heterogeneous catalysis: high catalytic activity and stereoselectivity with easy separation and convenient recycle. Based on this rationale we developed a new type of polymer-supported catalyst which offered better rate of reaction than the corresponding monomeric homogeneous catalyst while retaining the high stereoselectivity.[7] Soluble chiral polyester-supported BINAP ligands (**6** or **7**, Fig. 3) were synthesized by the polycondensation of (*S*)-5,5′-diamino-BINAP [(*S*)-**5**] or (*R*)-5,5′-diamino-BINAP [(*R*)-**5**], terephthaloyl chloride, and (2*S*,4*S*)-pentanediol in the presence of pyridine in dichloromethane (Fig. 3). The attachment of a chiral ligand to a soluble polymer support by copolymerization provided several key advantages: (1) facile control of the incorporation of BINAP in the polymer chains and (2) easy adjustment of the nature of the polymer matrix by using suitable comonomers. This approach offered an opportunity to

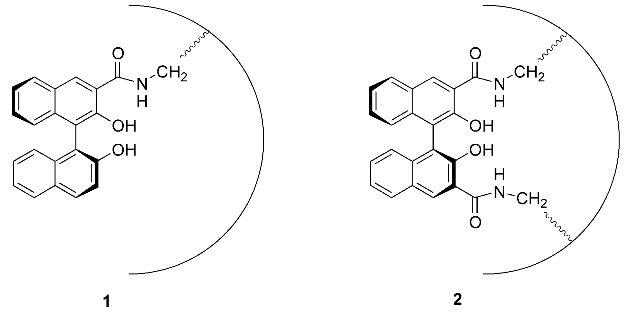


Figure 2.

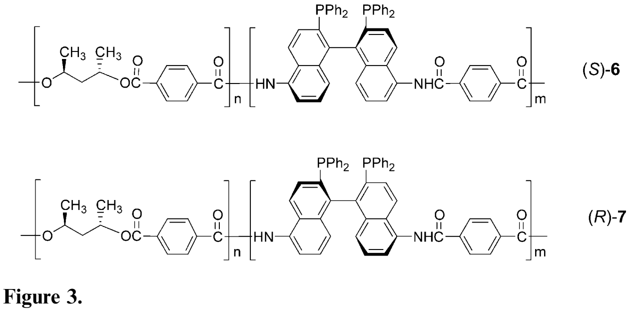


Figure 3.

Table 3. Studies of the polymer effect on the asymmetric hydrogenation of **8**[a]

Entry	Catalyst (prepared in situ)	Time (h)	Conv. (%[b])	ee (%[b])
1	**7** + [Ru(cymene)Cl_2]$_2$	18	100	92.9 (*R*)
2	**6** + [Ru(cymene)Cl_2]$_2$	12	97.4	93.6 (*S*)
3	**9** + [Ru(cymene)Cl_2]$_2$	36	99.8	93.5 (*S*)
4	(*S*)-BINAP + [Ru(cymene)Cl_2]$_2$	48	94.7	93.5 (*S*)
5	**6** + [Ru(cymene)Cl_2]$_2$	4	95.4	87.7 (*S*)
6	**9** + [Ru(cymene)Cl_2]$_2$	4	64.2	89.2 (*S*)
7	(*S*)-BINAP + [Ru(cymene)Cl_2]$_2$	4	56.5	88.7 (*S*)

[a] The hydrogenation was carried out in 0.026 M **8** in methanol–toluene (2:3, v/v) solution under the following conditions: Sub./Cat. = 200 (mol/mol); NEt_3/Sub. = 1:1 (mol/mol); H_2 = 110 kg/cm^2; reaction temperature = 1 ~ 2 °C except for entry 5 ~ 7 (temperature = rt).
[b] Determined by HPLC analysis using a Sumichiral OA-2500 column.

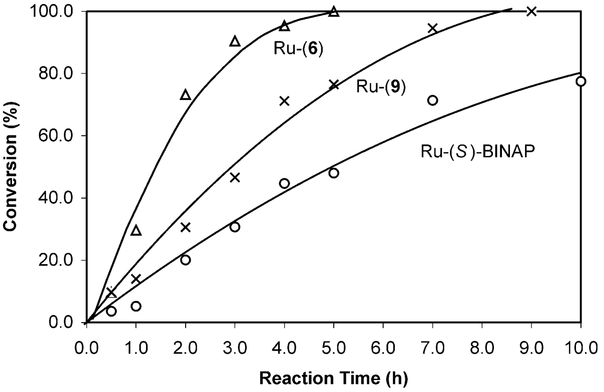
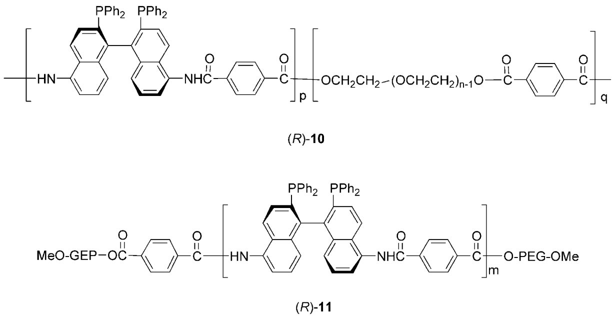


Figure 4. The comparison of the rates of hydrogenation catalyzed by Ru-(**6**), Ru-(**9**) and Ru-(*S*)-BINAP.

study the 'polymer effect' and to fine-tune the catalyst. This polymer-bound ligand was used in the Ru-catalyzed asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid (**8**). This catalyst showed high catalytic activity and enantioselectivity (Table 3). Repeated (10 times) recycling studies revealed that there was no loss of catalytic activity and enantioselectivity in the catalyst recycle. For the purpose of comparison, ligand **9** (5,5′-dibenzamido-BINAP) was synthesized as a homogeneous monomeric analogue of the polymer-supported ligand. The results of the comparison study are shown in Figure 4, which clearly reveal the positive influence of the support on catalytic activity.

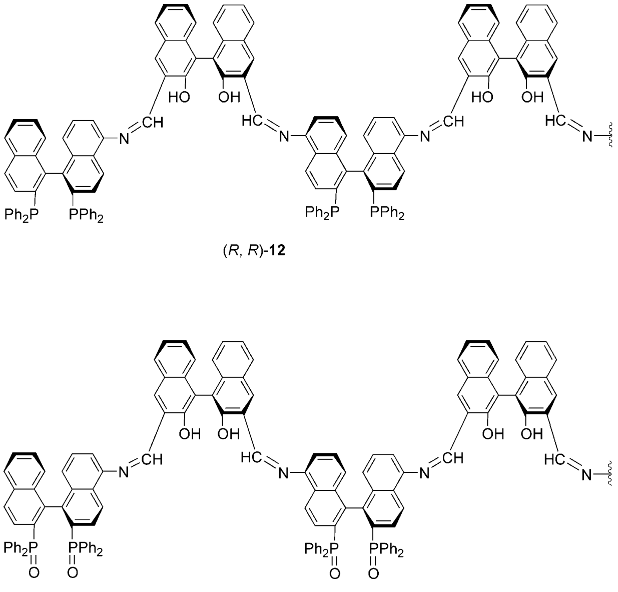
In order to improve the solubility of the polymer-bound BINAP ligand in methanol, which was found to be the best solvent for the hydrogenation of 2-arylacrylic acids, efforts were made to further modify the BINAP polymer ligand. MeO-PEG was chosen as co-support due to its commercial availability and its good solubility in organic solvents. Copolymer **10** and block polymer **11** (Fig. 5) were synthesized via condensation method as described above.[8] Both polymers were soluble in methanol, toluene, THF, methylene chloride and water, and the polymer was quantitatively recovered by precipitation in diethyl ether or *tert*-butyl methyl ether. These polymer ligands were studied for the Ru-catalyzed asymmetric hydrogenation of 2-arylacrylic acids both in methanolic solvent and in ethyl acetate/water two-phase system. The results showed that these new soluble polymeric catalysts exhibited high catalytic activity and enantioselectivity. When using methanol as solvent, enantiomeric excesses (ees) in the range of 90–96% were achieved which were slightly higher than those of Ru(BINAP) under the same reaction conditions. The polymer catalysts were tested in two recycle experiments and showed no loss of enantioselectivity and catalytic activity. In the two-phase hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid, Ru-**10** was found to have 30 times higher activity than the Ru(BINAP-4SO_3Na) catalyst,[9] which illustrated the advantage of the amphiphilic structure of the polymer ligand.



(*R*)-**10**

(*R*)-**11**

Figure 5.

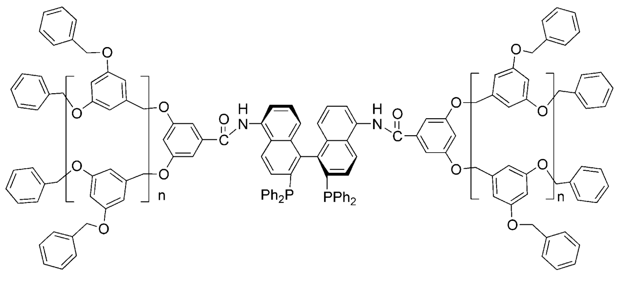


(*R*, *R*)-**12**

(*R*,*R*)-**13**

Figure 6.

We also studied the soluble bifunctional polymeric ligands (*R*,*R*)-**12** and (*R*,*R*)-**13** (Fig. 6) which were prepared via the direct condensation reaction of (*R*)-3,3′-diformyl-1,1′-bi-2-naphthol with (*R*)-5,5′-diamino BINAP (*R*)-**5** and with the diphosphine oxide (*R*)-5,5′-diamino BINAPO, respectively,[10] for asymmetric hydrogenation and diethylzinc addition to benzaldehyde. The different types of catalytic centers, BINOL/BINAP or BINOL/BINAPO, were alternatively organized in a regular chiral polymer chain. Both polymeric



(*R*)-**14**: **14a** n = 0; **14b** n = 1; **14c** n = 2

Figure 7.

ligands were found to be effective in the addition of diethylzinc to benzaldehyde either in the presence or in the absence of $Ti(O\text{-}^{i}Pr)_4$ with different enantioselectivities. After the reaction, the polymer ligand could be recovered by precipitation and maintained the same efficiency in successive uses. (*R*,*R*)-**12**/Ti(IV) catalyst, which showed similar efficiency as the parent catalyst BINOL/Ti(IV), was more enantioselective than (*R*,*R*)-**13**/Ti(IV). More interestingly, enhancement of the enantioselectivity was achieved by organizing these two types of catalytically active units, BINAPO and BINOL, in a regular polymer chain, in which polymer (*R*,*R*)-**13** gave the corresponding alcohol with 47.7% ee, albeit 13.6% ee for the 1:1 (mol ratio) mixture of BINOL and BINAPO system. Moreover, both polymer ligands showed to be higher effective than BINOL in the absence of $Ti(O\text{-}^{i}Pr)_4$. For example, polymer (*R*,*R*)-**12** gave the corresponding alcohol with 99.9% conversion and 38.0% ee, while BINOL gave only 19.0% conversion and 4.6% ee. (*R*,*R*)-**12** was also found to be effective in the Ru(II)-catalyzed asymmetric hydrogenation of 2-arylacrylic acids. The results demonstrated that the use of the copolymer catalyst rather than a mixture of monomer catalysts not only simplified the recycling of the catalyst, but also improved the enantioselectivity and/or the activity in certain cases.

Table 4. Activity and enantioselectivity in the asymmetric hydrogenation of 2-(*p*-isobutylphenyl)acrylic acid catalyzed by dendritic Ru(BINAP)[a]

Entry	Ligand	Time (h)	Conv.[b] (%)	TOF[c] (h^{-1})	ee[d] (%)
1	(*S*)-BINAP	2	10.2	6.3	89.8
2	**14a**	2	10.4	6.5	91.8
3	**14b**	2	13.2	8.3	92.6
4	**14c**	2	34.3	21.4	91.6
5	**14c**	5	69.3	17.3	91.6
6	**14c** (cycle 1)[e]	5	67.3	16.8	91.4
7	**14c** (cycle 2)[e]	5	68.9	17.2	91.8
8	**14c** (cycle 3)[e]	5	66.6	16.6	90.9

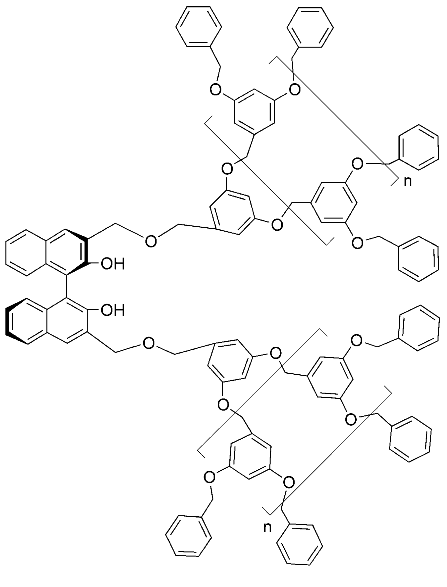
[a] Hydrogenations were carried out in 0.06 M solution of 2-(*p*-isobutylphenyl)acrylic acid using methanol/toluene (1:1, v/v) as solvent under the following reaction conditions: Sub./Cat. = 125 (mol/mol); NEt_3/Sub. = 3:2 (mol/mol); $H_2 = 80$ atom, rt.

[b] Based on GC analysis and ^1H NMR; all catalytic reactions reached 100% conversion in 24 h; (*R*)-form products were obtained except for entry 1 [(*S*)-form].

[c] Average TOFs calculated over the given reaction time.

[d] The ee values of the products were determined by GC with a Chrompak Chirasil-dex column (25 m×0.25 mm).

[e] The recovered catalyst was used.



(*R*)-**15**: **15a** n=0; **15b** n=1; **15c** n=2

Figure 8.

Dendrimer Chiral Catalyst[11]

Dendrimers are highly branched macromolecules having precisely defined molecular structures with nanoscale size. Since the pioneering work of van Koten et al. reported in 1994,[12] dendritic catalysts have triggered increasing attention.[13] Comparing with the linear soluble polymeric chiral catalysts, the dendrimer architecture may offer better control of the disposition of the catalytic specie(s) in soluble polymer-based catalysts. These catalysts can be removed from the reaction mixture by precipitation or by using membrane- or nanofiltration techniques. Such catalysts may fill the gap between homogeneous and heterogeneous catalysis and combine the advantages of both. In a recent study, we developed a series of effective and recyclable dendritic ligands (*R*-**14**, shown in Fig. 7) through the attachment of BINAP onto the core of the Fréchet-type dendrimer.[14] The asymmetric hydrogenation of 2-(*p*-isobutylphenyl)acrylic acid was used as a model reaction for the examination of the catalytic activity and enantioselectivity of these dendritic Ru(BINAP) catalysts. The sizes of the dendritic wedges were found to influence the reactivity of the ruthenium catalysts. Unlike the common dendritic catalysts, the rate of the reaction increased using higher generation catalysts. This effect was most pronounced when going from generation 2 to generation 3 (Table 4). The profound size effect is probably due to the steric bulk of the dendritic wedge which affects the dihedral angle of the two naphthalene rings in the Ru(BINAP) complex, and thus leads to different rate and/or enantioselectivity of the reaction. The dendritic Ru(BINAP) catalyst was quantitatively recovered by precipitation method and was reused in three cycles with essentially the same activity and enantioselectivity (Table 4).

Similarly, dendritic BINOL (**15**, Fig. 8) was also synthesized through the coupling of MOM-protected

Table 5. The asymmetric addition of diethylzinc to benzaldehyde catalyzed by (*R*)-BINOL and dendritic BINOL ligands in the absence of Ti(O^i-Pr)$_4$[a]

Entry	Ligand	Conv. (%)[b]	ee (%)[b]
1	(*R*)-BINOL	19.0	4.6
2	(*R*)-**15a**	97.5	61.9
3	(*R*)-**15b**	77.7	49.5
4	(*R*)-**15c**	79.8	48.6

[a] Benzaldehyde/ligand/ZnEt$_2$ = 1.0:0.2:3 (molar ratio), reaction temperature = 0 °C; solvent = toluene; reaction time = 7 h.

[b] Determined by chiral GLC analyses. The absolute configuration of product is in *R*-form.

3,3′-dihydroxymethyl-binaphthol and Fréchet's type polyether dendritic benzyl bromide followed by deprotection of MOM groups by TsOH.[15] The proximity of the dendritic wedges to the catalytic center also provided some different catalytic properties from BINOL in the enantioselective diethylzinc addition to benzaldehyde. In the absence of Ti(O^{i}Pr)$_4$, the dendritic chiral BINOL ligands showed much higher catalytic activity and enantioselectivity than BINOL (Table 5).

Several polymer-supported chiral catalysts based on the use of insoluble polymer, soluble polymer or dendrimer as supports have been prepared and tested for asymmetric catalysis. Higher catalytic activity/enantioselectivity than the corresponding monomeric homogeneous catalysts have been achieved through the rational design and adjustment of the polymer supports. The combined advantages of catalysis in homogeneous phase and facile separation by precipitation or ultrafiltration may open up a new area for active research and attractive commercial application.

Acknowledgements

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