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Polystyrene-Supported TRIP: A Highly Recyclable Catalyst for Batch and Flow Enantioselective Allylation of Aldehydes

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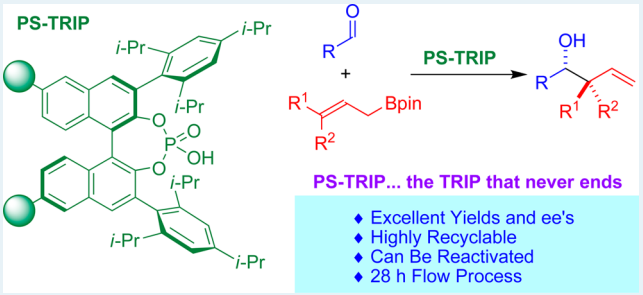
Supporting Information

ABSTRACT: The widely applicable TRIP phosphoric acid catalyst has been immobilized on polystyrene using a copolymerization-based strategy. The resin (**PS-TRIP**) has proven to be highly active and enantioselective in the asymmetric allylboration of aldehydes. Moreover, it has shown to be extremely robust, as it can be reused for 18 times, after which it still retained its activity. Lastly, to further prove the benefits of the immobilization, a continuous flow experiment spanning 28 h has been carried out with very high yields and ee's.



KEYWORDS: *enantioselective catalysis, chiral phosphoric acids, polystyrene-supported catalysts, flow chemistry, organocatalysis*

1. INTRODUCTION

Since the pioneering works of Akiyama[1] and Terada,[2] chiral phosphoric acids have proven to be extremely successful and versatile enantioselective catalysts.[3] Indeed, these Brønsted acids (which can be regarded as a metal-free alternative to chiral Lewis acids) have been used in a wide variety of asymmetric catalytic transformations including transfer hydrogenation,[4] addition to imines,[5] multicomponent reactions,[6] or (trans)-acetalization,[7] to name just a few. With BINOL-derived phosphoric acids, the substituents in the 3,3′ positions have been found to exert a dramatic effect on both the catalytic activity and enantioselectivity.[8] Among all the reported structures, the 2,4,6-tris-isopropyl derivative commonly known as TRIP (introduced by List et al. in 2005[4a]) has been the most successful, judging by the recent literature. This catalyst has been applied to a vast range of enantioselective reactions with unprecedented levels of stereocontrol,[9] either as a Brønsted acid catalyst or in ACDC catalysis.[10] However, TRIP presents some important drawbacks, mainly associated with its tedious preparation (reflected in a high cost), the adventitious formation of the related sodium or calcium salts,[11] and the usually high catalyst loadings required.

Thus, even if it might entail a somewhat longer sequence, we thought it could be interesting to study the immobilization[12] of TRIP onto a solid support as it would allow us to (a) recover and reuse the catalyst, thus reducing its effective cost and (b) preclude the formation of calcium or sodium salts by skipping any chromatographic purification. On the basis of the few previous works involving solid-supported phosphoric acids,[13,14] (including our own experience[15]), we expected that a polystyrene-supported TRIP (**PS-TRIP**) would fulfill these conditions while retaining the excellent enantiocontrol and wide applicability of its homogeneous counterpart (Figure 1). However, to the best of our knowledge, the only reported attempt to immobilize TRIP had given rise to a nonactive catalyst,[16] and thus, the immobilization strategy was deemed to be crucial.

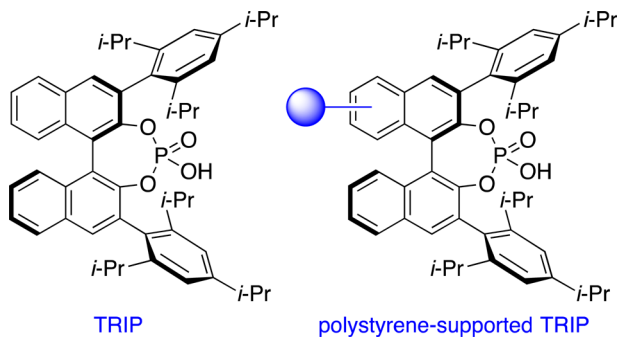


Figure 1. TRIP catalyst and an immobilized version thereof.

We report herein the development of a simple and effective strategy for the incorporation of TRIP in a slightly cross-linked polystyrene network without compromising the excellent catalytic activity and enantioselectivity displayed by the monomer. The resulting functional polymer (**PS-TRIP**) has been used as an abundantly recyclable catalyst for the highly enantioselective allylboration of aldehydes in batch and flow.

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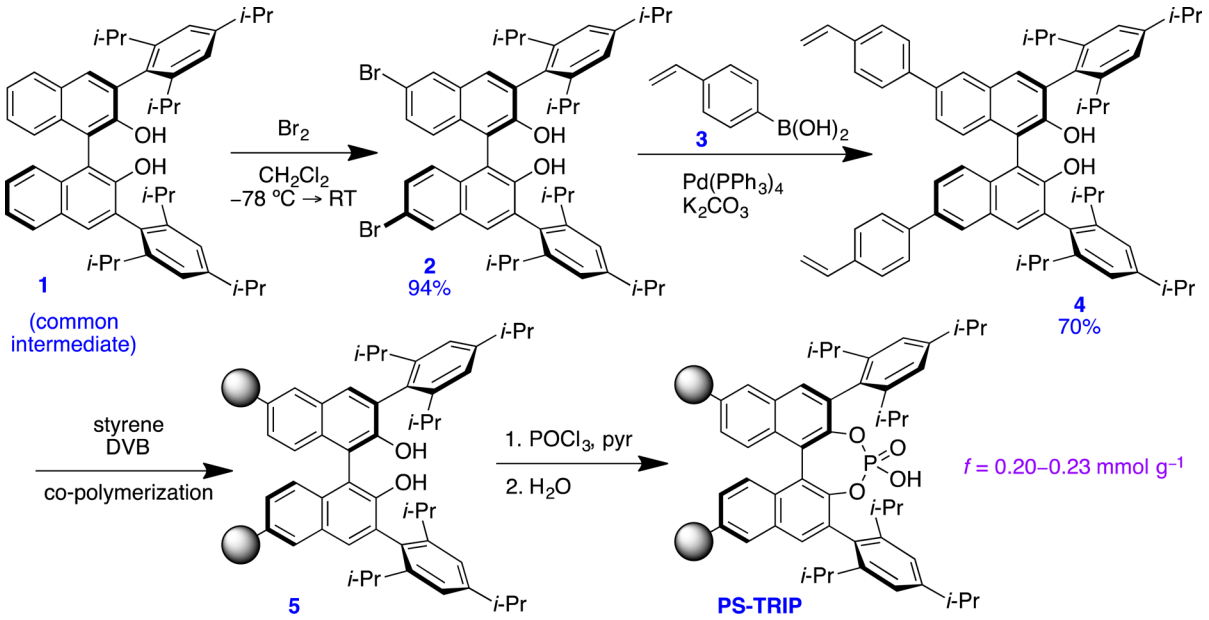
Scheme 1. Preparation of PS-TRIP



2. RESULTS AND DISCUSSION

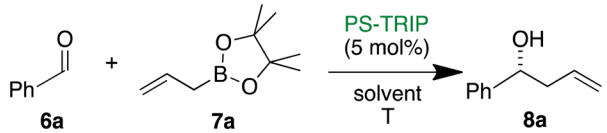
The preparation of **PS-TRIP** (Scheme 1) is common to that of its homogeneous analogue[11] until diol **1**. At that point, instead of the direct phosphorylation reported by List and co-workers, we carried out a dibromination in 6,6′, followed by Suzuki coupling with 4-vinylphenylboronic acid (**3**). Divinylated compound **4**, with a conveniently modified BINOL scaffold, was then copolymerized with styrene and divinylbenzene to generate resin **5**,[17] which was in turn phosphorylated to generate **PS-TRIP**.

The synthesis proved to be very reproducible, leading in all cases to functionalization levels (determined by elemental analysis of P) of 0.20−0.23 mmol g^{-1}. Remarkably, the whole sequence involves only three more steps than the route for the homogeneous TRIP and both the bromination and the Suzuki coupling are very high yielding.

After optimizing the synthesis, we set our sights in finding a benchmark reaction to put the new catalytic resin **PS-TRIP** to the test. We envisaged that the asymmetric allylboration of aldehydes reported by Antilla et al.[18] might be an interesting choice, given the versatility of chiral homoallylic alcohols as building blocks in synthesis and the simplicity of the reaction protocol. To our delight, working with 10 mol % **PS-TRIP** in toluene at 0 °C, the reaction between benzaldehyde and allylboronic pinacol ester gave **8a** in excellent yield and enantioselectivity (Table 1, entry 1). Lowering the catalyst loading to 5 mol % allowed us to reach similar results (entry 2), whereas changing the solvent resulted in lower ee's (entries 3−5). If the reaction was cooled to −30 °C, the result with benzaldehyde was affected minimally (entry 6), but more electrophilic aldehydes gave better ee's. We attribute this to a noncatalyzed background reaction, and thus, in order to minimize this unwanted process, we decided to carry out the rest of the scope at −30 °C. Lastly, when concentration was increased to 0.1 M, the reaction turned out to be much faster while maintaining yield and ee (entry 7).

Once the reaction parameters had been fine-tuned (5 mol % **PS-TRIP**, 0.1 M in toluene, −30 °C, 6 h), we decided to study the scope of the reaction. Thus, a wide range of aldehydes was

Table 1. Screening of Reaction Conditions[a]



entry	solvent	T (°C)	t (h)	yield (%)	ee (%)
1[b]	toluene	0	16	89	96
2	toluene	0	16	92	94
3	THF	0	48	traces	n.d.
4	CH_2Cl_2	0	16	90	88
5	EtOAc	0	48	67	52
6	toluene	−30	16	97	95
7[c]	toluene	−30	6	96	95

[a]Reactions carried out at a concentration of 0.06 M with 5 mol % **PS-TRIP** and 1.2 equiv of **7a**. [b]With 10 mol % **PS-TRIP**. [c]Concentration: 0.1 M.

submitted to these conditions (18 examples), the results being summarized in Scheme 2. **PS-TRIP** proved to be excellent in the catalytic preparation of highly enantioenriched homoallylic alcohols. Electron-poor and electron-rich aromatic aldehydes (products **8a−o**) are generally well-tolerated, giving rise to outstanding yields and enantioselectivities (up to 96% ee). *ortho*-Halogenated derivatives seem to be the exception, giving rise to only moderate ee's (products **8e,j**). In contrast, a toluidine with the same substitution pattern (product **8o**) reached up to 95% ee, indicating that the results with *o*-halobenzaldehydes likely arise from a combination of steric and electronic factors. Heteroaromatic substituents like 3-furyl (product **8l**) gave very good results, whereas use of a 3-pyridine resulted in a completely racemic product (**8k**); this is probably due to the basicity of this heteroaromatic moiety, which might interact with the phosphoric acid in **1**. Other interesting substrates include an α,β-unsaturated aldehyde (product **8p**), a linear one (product **8q**), and isophthalaldehyde, which gave rise to the C_2-symmetric product **8r** through double allylation.

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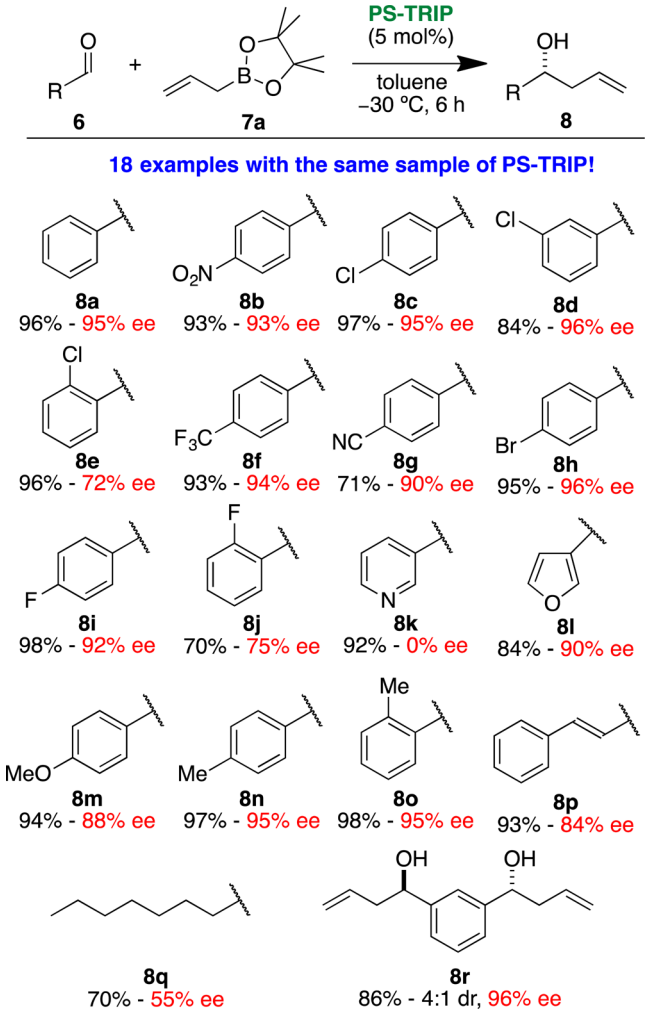
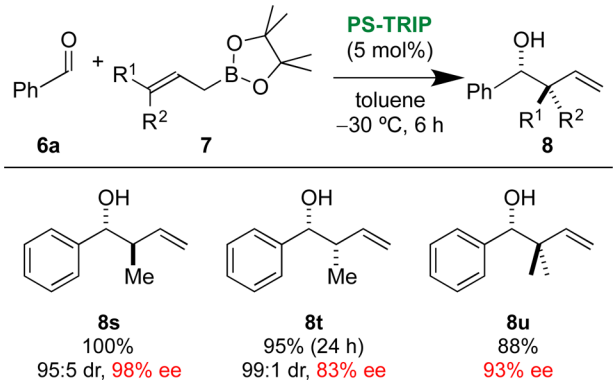
Scheme 2. Aldehyde Scope[a]



[a]All reactions were carried out with the same sample of PS-TRIP (recycled after each run).

Scheme 3. Scope of the Allylating Partner



However, perhaps the most remarkable feature of the catalyst is that all the scope shown in Scheme 2 (18 examples) has been run with the same sample of **PS-TRIP**, which has been reused extensively showing no decay in activity.

Indeed, at the end of the scope, benzaldehyde was allylated again, completely replicating the results obtained at the beginning. This shows the outstanding robustness of **PS-TRIP**, which can be quantified in an accumulated TON of 321. Even more interestingly, during this process, the catalyst did lose activity a couple of times (e.g., after running the test with 3-pyridinecarboxaldehyde), but simply washing the resin with a solution of HCl in EtOAc led to a complete recovery of the catalytic activity. The allylating partner scope was also briefly studied, giving excellent results in the *trans*-crotylation and dimethylallylation of benzaldehyde (products **8s** and **8u**, Scheme 3). The *cis*-crotylboronic derivative gave a slower reaction, thus providing somewhat decreased enantioselectivity, perhaps due to a competitive background reaction. However, **8t** was still isolated in 83% ee.

Encouraged by the excellent results displayed by **1**, we decided to study the related flow process.[19] A preliminary batch test showed that **8a** gave similar results at RT and at −30 °C, so we decided to carry out this flow experiment at 25 °C for the sake of simplicity. To this end, the three-pump system outlined in Figure 2 was assembled. As depicted, a packed bed reactor containing **PS-TRIP** was fed with two solutions containing the aldehyde and the allylboronic ester. Downstream of the column, an aqueous solution of $NaHSO_3$ was used to scavenge any unreacted aldehyde. Preliminary attempts to run the flow experiment without this last step resulted in good enantioselectivities in aliquots taken from the outstream but somewhat diminished ee's on the collected product. We attribute this observation to a background reaction taking place in the collecting flask between the excess allylboronic ester and the small amounts of aldehyde remaining in the outstream.

Under these conditions, the flow experiment was kept running for 28 h, after which 4.60 g of **8a** were isolated (92% yield, 91% ee). These numbers amount to a total TON of 282 and a productivity of 2.22 mmol h^{-1} g_{resin}^{-1}. Remarkably, no detectable decrease in the catalytic activity of the resin took place in the 28 h experiment. This fact, together with the easy reactivation of **PS-TRIP** allows visualizing the small cartridge containing only 0.5 g of catalyst as a micropilot plant, suitable for the production of decimol amounts of enantiopure homoallylic alcohol in short periods of time (ca. 90 h) with highly reduced energy costs (no cooling required) and material costs (in a flow process with a nondeactivating catalyst, the TON increases linearly with time). Even more interestingly, catalyst cartridges involving 5 to 50 g of PS-TRIP (amounts within reach of the procedure reported herein) could be used for kilogram production under very favorable cost and safety conditions.

3. CONCLUSIONS

In summary, we have prepared a polystyrene-supported TRIP catalyst that has proven to be very active and enantioselective in the allylation of aldehydes. The synthetic route, which involves the copolymerization of a vinylated analogue of the TRIP diol, requires only three more steps than that of the homogeneous counterpart and is amenable to multigram production. The slightly longer synthesis is exceedingly compensated by the high recyclability of **PS-TRIP**, which has given accumulated TONs in batch as high as 321 (the catalyst was still active after 18 runs). The catalytic resin has also been put to the test by means of a flow experiment spanning 28 h, in which 4.60 g of allylated product were obtained (TON of 282, productivity of 2.22 mmol h^{-1} g_{resin}^{-1}) without a decrease in activity. Thus, we believe that the recyclability and robustness of **PS-TRIP** make it an interesting alternative to the already successful homogeneous version.

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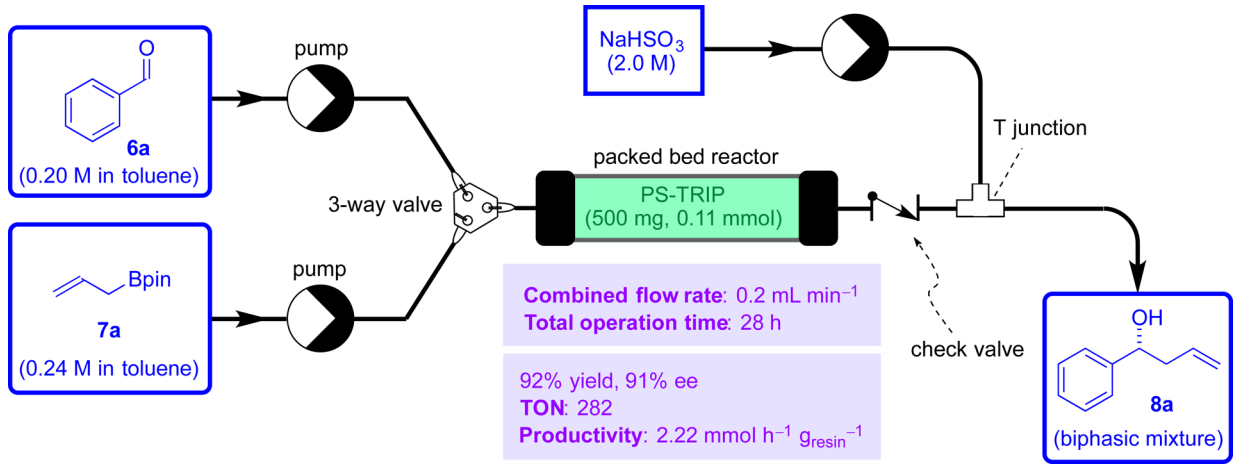

Figure 2. Experimental setup for the continuous flow catalytic enantioselective allylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02621.

Synthetic procedures, characterization data, copies of NMR spectra, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568.

(2) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

(3) For reviews, see: (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047–9153. (b) Lv, F.; Liu, S.; Hu, W. *Asian J. Org. Chem.* **2013**, *2*, 824–836. (c) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (d) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262–5276. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010. (f) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909–3912.

(4) (a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424–7427. (b) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781–3783. (c) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683–3686. (d) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562–4565. (e) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852–865. (f) Aillerie, A.; Talancé, V. L. d.; Moncomble, A.; Bousquet, T.; Pélinski, L. *Org. Lett.* **2014**, *16*, 2982–2985.

(5) (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805. (b) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065–1068. (c) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484–1485. (d) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609–2611. (e) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399–402. (f) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731–1734. (g) Li, G.; Kaplan, M. J.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1960–1963. (h) Enders, D.; Seppelt, M.; Beck, T. *Adv. Synth. Catal.* **2010**, *352*, 1413–1418.

(6) (a) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458–2462. (b) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599. (c) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804–14813. (d) He, L.; Bekkaye, M.; Retailleau, P.; Masson, G. *Org. Lett.* **2012**, *14*, 3158–3161. (e) Brioche, J.; Courant, T.; Alcaraz, L.; Stocks, M.; Furber, M.; Zhu, J.; Masson, G. *Adv. Synth. Catal.* **2014**, *356*, 1719–1724.

(7) (a) Čorić, I.; Müller, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 17370–17373. (b) Čorić, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536–8537. (c) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074–8077. (d) Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 12932–12936. (e) Khomutnyk, Y. Y.; Argüelles, A. J.; Winschel, G. A.; Sun, Z.; Zimmerman, P. M.; Nagorny, P. *J. Am. Chem. Soc.* **2016**, *138*, 444–456.

(8) Reid, J. P.; Goodman, J. M. *J. Am. Chem. Soc.* **2016**, *138*, 7910–7917.

(9) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31–39.

(10) (a) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193–4195. (b) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369. (c) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119–1122. (d) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071. For a review, see: (e) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518–533.

(11) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189–2192.

(12) For reviews on immobilization of (enantioselective) catalysts, see: (a) Benaglia, M. *Recoverable and Recyclable Catalysts*; Wiley-VCH: Weinheim, 2009. (b) De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, 2000. (c) Zamboulis, A.; Moitra, N.; Moreau, J. J. E.; Cattoën, X.; Wong Chi Man, M. *J. Mater. Chem.* **2010**, *20*, 9322–9338. (d) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367–1390. (e) Lu, J.; Toy, P. H. *Chem. Rev.* **2009**, *109*, 815–838. (f) Kristensen, T. E.; Hansen, T. *Eur. J. Org. Chem.* **2010**, 3179–3204. (g) Benaglia, M. *New J. Chem.* **2006**, *30*, 1525–1533. (h) Trindade, A. F.; Gois, P. M. P.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 418–514. (i) Corma, A.; Garcia, H. *Adv. Synth. Catal.* **2006**, *348*, 1391–1412. (j) Gruttadauria, M.; Giacalone, F.; Noto, R. *Chem. Soc. Rev.* **2008**, *37*, 1666–1688.

DOI: 10.1021/acscatal.6b02621
ACS Catal. 2016, 6, 7647–7651

(13) (a) Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Adv. Synth. Catal.* **2010**, *352*, 281−287. (b) Bleschke, C.; Schmidt, J.; Kundu, D. S.; Blechert, S.; Thomas, A. *Adv. Synth. Catal.* **2011**, *353*, 3101−3106. (c) Kundu, D. S.; Schmidt, J.; Bleschke, C.; Thomas, A.; Blechert, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5456−5459.
(14) For reviews, see: (a) Mutyala, A. K.; Patil, N. T. *Org. Chem. Front.* **2014**, *1*, 582−586. (b) Rodríguez-Escrich, C. *Chim. Oggi* **2015**, *33*, 12−15.
(15) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Chem. - Eur. J.* **2014**, *20*, 2367−2372.
(16) Mayer-Gall, T.; Lee, J.-W.; Opwis, K.; List, B.; Gutmann, J. S. *ChemCatChem* **2016**, *8*, 1428−1436.
(17) (a) Itsuno, S.; Watanabe, K.; Koizumi, T.; Ito, K. *React. Polym.* **1995**, *24*, 219−227. (b) Sherrington, D. C. *Chem. Commun.* **1998**, 2275−2286. (c) Besenius, P.; Cormack, P. A. G.; Liu, J.; Otto, S.; Sanders, J. K. M.; Sherrington, D. C. *Chem. - Eur. J.* **2008**, *14*, 9006−9019. (d) Sagamanova, I.; Rodríguez-Escrich, C.; Molnár, I. G.; Sayalero, S.; Gilmour, R.; Pericàs, M. A. *ACS Catal.* **2015**, *5*, 6241−6248. (e) Llanes, P.; Sayalero, S.; Rodriguez-Escrich, C.; Pericas, M. A. *Green Chem.* **2016**, *18*, 3507−3512.
(18) For the seminal paper, see: (a) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884−11886. For related work in phosphoric acid-catalyzed allylation/propargylation of aldehydes, see: (b) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391−1394. (c) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 10947−10952. (d) Reddy, L. R. *Org. Lett.* **2012**, *14*, 1142−1145. (e) Reddy, L. R. *Chem. Commun.* **2012**, *48*, 9189−9191. (f) Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 1208−1215. (g) Incerti-Pradillos, C. A.; Kabeshov, M. A.; Malkov, A. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 5338−5341. (h) Rodríguez, E.; Grayson, M. N.; Asensio, A.; Barrio, P.; Houk, K. N.; Fustero, S. *ACS Catal.* **2016**, *6*, 2506−2514.
(19) (a) Bräse, S.; Lauterwasser, F.; Ziegert, R. E. *Adv. Synth. Catal.* **2003**, *345*, 869−929. (b) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem. - Eur. J.* **2006**, *12*, 5972−5990. (c) Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein J. Org. Chem.* **2009**, *5*, 19. (d) Puglisi, A.; Benaglia, M.; Chiroli, V. *Green Chem.* **2013**, *15*, 1790−1813. (e) Zhao, D.; Ding, K. *ACS Catal.* **2013**, *3*, 928−944. (f) Tsubogo, T.; Ishiwata, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 6590−6604. (g) Atodiresei, I.; Vila, C.; Rueping, M. *ACS Catal.* **2015**, *5*, 1972−1985. (h) Rodríguez-Escrich, C.; Pericàs, M. A. *Eur. J. Org. Chem.* **2015**, 1173−1188.

DOI: 10.1021/acscatal.6b02621
ACS Catal. 2016, 6, 7647−7651