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## Accepted Article

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# Silicon-based Bulky Group–Tuned Parallel Kinetic Resolution in Copper-Catalyzed 1,3-Dipolar Additions

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**Abstract.** The development of new strategies or reaction processes that tease new reactivity of functional groups continues to spur synthetic chemists toward innovative solutions that access new compounds. Herein, we find that the silicon-based bulky group enables a 1,3-dipolar addition–initiated parallel kinetic resolution (PKR) to occur unexpectedly, leading to the highly enantioselective synthesis of two structurally different types of amino acid derivatives via chemodivergent [3+2] cycloaddition reactions and tandem conjugate addition-elimination reaction respectively. The resulting and structurally divergent enantioenriched amino acid derivatives that contain four contiguous stereogenic centers and an all-carbon quaternary center were obtained with up to 99% *ee* with >95:1 *dr* and good yields.

**Keywords:** Kinetic resolution; organosilicon; 1,3-dipolar cycloaddition; chiral ligand; copper.

Efficient kinetic resolution (KR) is widely used method to obtain enantioenriched products from racemic materials, and continue to play a critical or practical role in chiral synthesis.[1] Traditional kinetic resolution that based on an unequal reaction rate of each enantiomer gives a maximum of 50% product, in which the enantioenriched stating material is recovered or another enantiomer remains unchanged.[2] As an alternative to kinetic resolution, parallel kinetic resolution (PKR)[3,4] provided an attracting and useful process to stereoselective and structurally divergent synthesis of chiral compounds, in which both enantiomers of the starting material react with a reagent to give distinct products with high enantiomeric excess.[5] Recently, much interest has been devoted to PKR[6], where a really impressive example is Bode's PKR based on flow chemistry and polymer-supported pseudoenantiomeric acylating agents. Interestingly, rhodium catalysts were proved to be worked well to create parallel kinetic resolution of different compounds via cycloisomerization[7a], hydroarylations[7b], cyclopropanation/cope rearrangement[7c] or [4+2] annulation of 4-alkynals with isocyanates[7d]. Notably, except rhodium catalysis, there are few methods focused on metal-catalyzed transformations in the field of PKR. Therefore, it is rewarding to exploit a powerful PKR via rational design of functional group-based transformation in order to improve enantioselection by kinetic resolution.

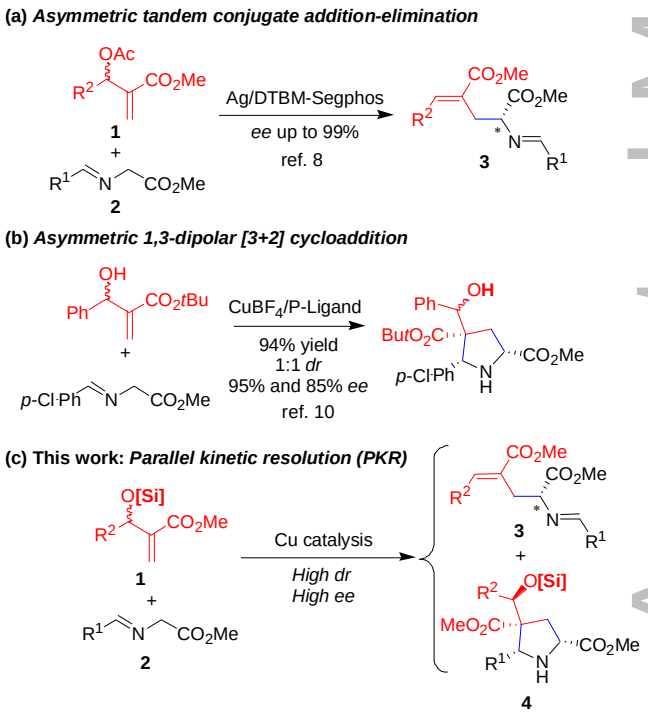


**Figure 1**. Silicon-based bulky group (SBG) -tuned parallel kinetic resolution: 1,3-Dipolar addition-initiated [3+2] cycloaddition reaction and tandem conjugate addition-elimination reaction.

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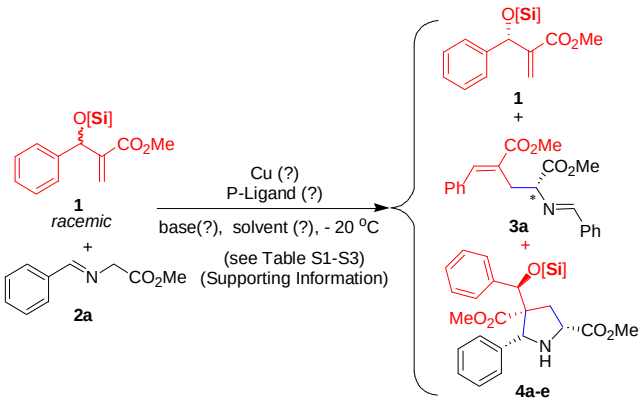
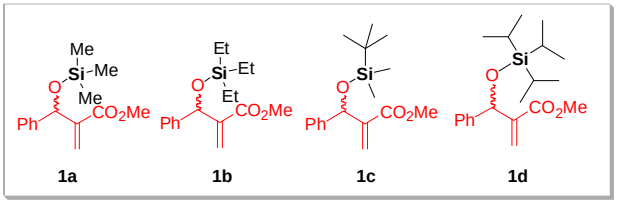
Very recently, our group described a silver-catalyzed [3+2] cycloaddition of various glycine aldimino esters with activated alkenes[8a-d] and asymmetric tandem conjugate addition-elimination reaction of glycine aldimino esters with racemic Morita-Baylis-Hillman (MBH) adducts (MBH acetates) that though 1,3-dipolar activation (Figure 1, equation a)[8e], allowing for facile preparation of a variety of glutamic acid derivatives in high ee values (up to 99% *ee*). Although the racemic MBH acetates are ideal model compounds in PKR chemistry, we did not detect another 1,3-dipolar [3+2] cycloaddition reaction except tandem conjugate addition-elimination reaction in this work. Very surprisingly, racemic MBH adducts have seldom been employed as activated alkenes in catalytic asymmetric [3+2] cycloaddition reactions. Although numerous reports on highly chemo-, diastereo-, and enantio-selective [3+2] cycloaddition of azomethine ylides with activated olefins have been achieved in the past decade[9], to date, only one example has been documented by Wang and co-workers[10], in which they found the racemic Morita–Baylis–Hillman adduct could be applie in 1,3-dipolar [3+2] cycloaddition reaction with the azomethine ylide to give two diastereomers in 94% yield and excellent enantioselectivities (95% *ee* and 85% *ee*) but with 1:1 diastereoselectivity (Figure 1, equation b). Distinct from these findings, we envisioned that the introduction of silicon-based bulky group[11] into the racemic MBH adducts could tune the reactivity and stereoselectivity of MBH adducts in the intermolecular cycloaddition and PKR of more stable MBH-derived silyl ethers with glycine aldimino esters is also possibly to be established for the enantioselective construction of biologically attractive and multi-substituted heterocycles bearing four contiguous stereogenic centers and an all-carbon quaternary center.

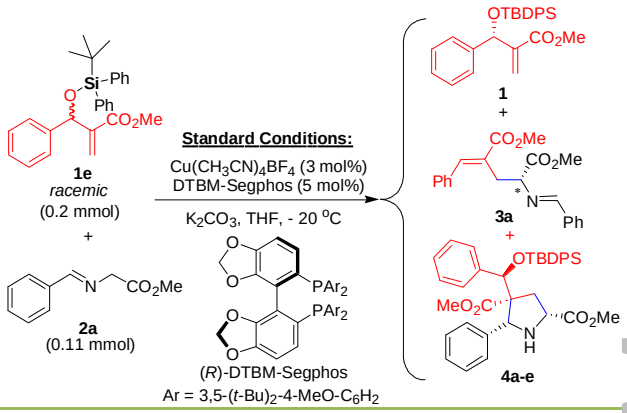



**Scheme 1**. Kinetic resolution of racemic MBH-derived silyl ether **1a-1e** by screening of various catalyst systems and chiral ligands: Effect of silicon-based bulky group on the copper-catalyzed reaction of **1** and **2**.

Herein, we reported an unprecedented and highly enantioselective copper-catalyzed [3+2] cycloaddition of racemic Morita-Baylis-Hillman (MBH) adducts with glycine aldimino esters that tuned by silicon-based bulky group –initiated steric repulsion and catalyst-substrate interaction. In addition, it is a novel parallel kinetic resolution approach to highly substituted pyrrolidine derivatives and glutamic acid derivatives via chemodivergent [3+2] cycloaddition and tandem conjugate addition-elimination reaction (Figure 1, equation c).

**Table 1.** Control experiments for intermolecular reaction of MBH adducts **1** with glycine aldimino ester **2a**.




| Entry | Variations from the standard conditions | Yield (%)[a] | **4a-e** | |
|---|---|---|---|---|
| | | | *dr*[a] | *ee*(%)[b] |
| 1 | no | 34 | 95/5 | 99/99 |
| 2 | **1a** instead of **1e** | 51 | 84/16 | 98/99 |
| 3 | **1b** instead of **1e** | 35 | 74/26 | 99/99 |
| 4 | **1c** instead of **1e** | 34 | 75/25 | 99/99 |
| 5 | **1d** instead of **1e** | 26 | 88/12 | 99/99 |
| 6 | 1 equiv of **2a** instead of 0.55 equiv[c] | 42 | 95/5 | 99/99 |
| 7 | 0 °C instead of -20 °C[d] | 36 | 96/4 | 99/99 |

Note: [a] The yield and *dr* value of **4** was determined by NMR analysis. [b] The *ee* value of two enantiomers was determined by chiral HPLC. [c] The 40% of product **3a** was detected in this case. [d] Based on the condition of entry 6.

Our initial investigations started by the kinetic resolution of racemic MBH-derived silyl ether **1a** by screening of various catalyst systems and chiral ligands (Scheme 1 and see Supporting Information). When the reaction of racemic MBH-derived silyl ether (**1a**) with glycine aldimino ester (**2a**) was carried out using 3 mol % $Cu(CH_3CN)_4BF_4$ and 5

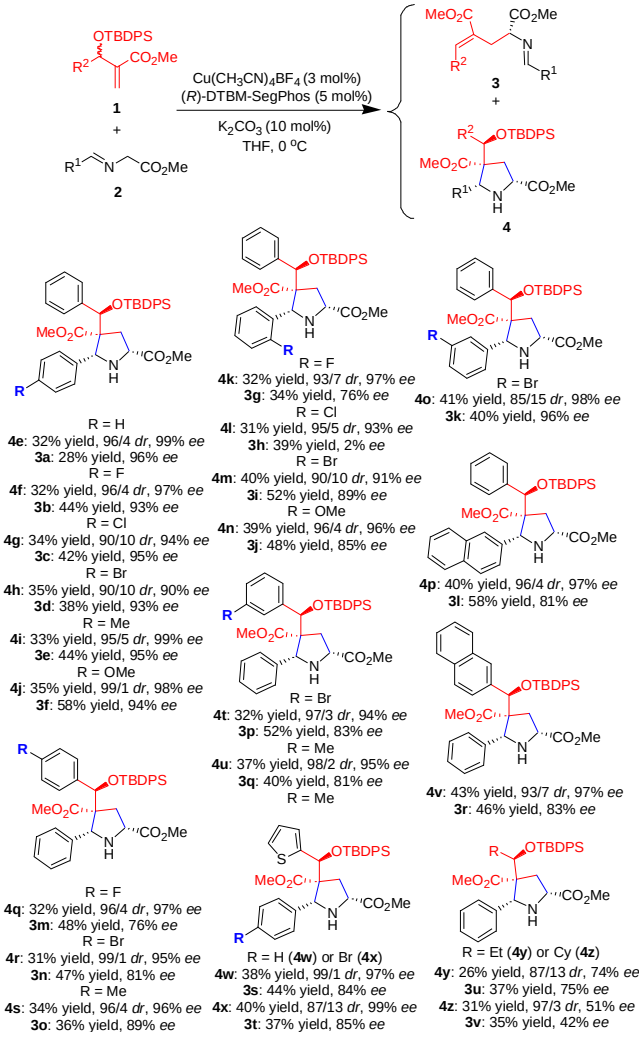
mol% P-ligand in THF at -20 °C, enantioselective [3+2] cycloaddition reaction proceeded smoothly to give product **4a** in good yields (Table S1, see Supporting Information). Among different phosphine ligands, the DTBM-Segphos (*see* Table 1) was the most efficient ligand and afforded the desired adduct **4a** with good diastereoselectivity (84/16 *dr*) and excellent enantioselectivity (98% *ee* for major isomer and 99% *ee* for minor isomer) and enantioenriched MBH-derived silyl ether **1a** by kinetic resolution. The use of $Cu(CH_3CN)_4PF_6$ as a catalyst was similarly effective (see Table S2 of Supporting Information, 50% conversion, 84/16 *dr*, and 98% *ee* and 99% *ee* for two enantiomers), and interestingly, the reaction performed with AgOAc also provided **4a** in 53% yield (see Table S2, 77/23 *dr*, and 98% *ee* for both enantiomers). However, these catalysts still exhibit inferior activity in this reaction in comparison to that of $Cu(CH_3CN)_4BF_4$ in term of diastereoselectivity and enantioselectivity of all the products. And the screening of various bases for the copper-catalyzed [3+2] cycloaddition reaction, $K_2CO_3$ should be the best choice (See Table S3 of Supporting Information). Based on the observation that $Cu(CH_3CN)_4BF_4$ combined with DTBM-Segphos undergo highly enantioselective [3+2] cycloaddition of MBH-derived silyl ether **1a** with glycine aldimino ester **2a** at mild reaction conditions, whereas the recovered MBH-derived silyl ether are normally obtained with moderate *ee* values, we hypothesized that the introduction of silicon-based bulky group to MBH-derived silyl ethers may allow highly efficient kinetic resolution or [3+2] cycloaddition reaction from racemic MBH-derived silyl ethers. Therefore, we began by exploring the effect of silicon-based bulky group on the copper-catalyzed [3+2] cycloaddition by kinetic resolution under the optimized reaction conditions (Table 1).

As shown in Table 1, the TBDPS-containing racemic MBH-derived silyl ether (**1e**) did lead to product **4e** with excellent diastereoselectivity (95:5 *dr*) and excellent enantioselectivity (99% *ee*), but when other silicon-based bulky groups were used, product **4a** was obtained with almost the same level of diastereoselectivity, albeit the enantioselectivity is also excellent in each case. Notably, the recovered starting material **1** was obtained with varying degrees of enantioselectivity, which prompted us to examine the [3+2] cycloaddition of TBDPS-containing MBH-derived silyl ether (**1e**) with an equal amount of glycine aldimino ester **2a**. Gratifying, a parallel kinetic resolution was confirmed in this case, in which two different enantiomers with high ee values (93% *ee* of **3a** and 99% *ee* of **4e** respectively) were obtained synchronously by asymmetric 1,3-dipolar [3+2] cycloaddition reaction and tandem conjugate addition-elimination reaction of glycine aldimino ester **2a** with MBH-derived silyl ether **1e** (Table 1, entry 7). This outcome represents the first Cu-promoted parallel kinetic resolution based on 1,3-dipolar [3+2] cycloaddition reaction of glycine aldimino ester with MBH-derived silyl ether under mild conditions. We also discovered that the parallel kinetic resolution process completed within 12 h at room temperature or 0 °C in THF and other solvents gave negative effect on the diastereoselectivity or conversion (Table S5). Finally, it deserves mentioning that this catalytic asymmetric transformation provides a facile approach to the enantioselective construction of pyrrolidines bearing four contiguous stereogenic centers and featuring a quaternary stereocenter.

To further expand the synthetic utility of this silicon-based bulky group (TBDPS) –tuned parallel kinetic resolution, the 1,3-dipolar [3+2] cycloaddition/tandem conjugate addition-elimination reaction was examined with diverse glycine aldimino esters and MBH-derived silyl ethers generated from a series of aldehydes and glycine (Scheme 2). As expected, various MBH-derived silyl ethers with different substituents underwent the parallel kinetic resolution in moderate to good yield (60–98%). Almost all substrates furnished the enantioenriched glutamic acid derivatives **3** (up to 95% *ee*) and highly substituted pyrrolidines**4**, albeit yielding diastereomeric mixtures (from 87:13 to 99:1). Pleasingly, all the aromatic MBH-derived silyl ether substrates undergoes the 1,3-dipolar [3+2] cycloaddition process with glycine aldimino esters in good enantioselectivities to generate the substituted pyrrolidines **4** with four contiguous stereogenic centers. Except the aliphatic MBH-derived silyl ether, the enantioselectivities of pyrrolidines **4** were slightly independent of the electronic properties of substituents in the 1,3-dipolar [3+2] cycloaddition process, with a narrow range from 91% *ee* to 99% *ee*. Substrates with electron-rich aromatic substrates on para-position of arenes were more reactive than that on *ortho*-position. *meta*-Substituted MBH-derived silyl ethers also reacted selectively with glycine aldimino ester in this 1,3-dipolar [3+2] cycloaddition process. The tandem conjugate addition-elimination reaction is sensitive to substituents in the *ortho*-position and no enantioselectivity was obtained when *o*-chloro -substituted glycine aldimino ester was used in this reaction. This fact was in agreement with the parallel kinetic resolution that had similar $k_{A(R)} \approx k_{A(S)}$ rates (preferably identical) and occurred without mutual interferences. Due to the certain enantiomer -directed [3+2] cycloaddition, the enantioselectivity of product would be varied from low to high enantioselectivity via tandem conjugate addition-elimination reaction, that different from previous silver-catalyzed asymmetric tandem conjugate addition-elimination reaction of glycine aldimino esters with racemic MBH adducts.[8] Notably, aliphatic substituents was also found to have a significant influence on the stereoselectivity and reactivity, for example, when methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylenepentanoate (Et-substituted MBH-derived silyl ether) or methyl 2-((*tert*-butyldiphenylsilyloxy)(cyclohexyl)methyl)-acrylate (Cy-substituted MBH-derived silyl ether) was utilized, the reaction occurred smoothly in good yield and diastereoselectivity but with decreased enantioselectivity (Scheme 2). Even though, we were pleased to observe that various aromatic MBH-derived silyl ethers and glycine aldimino esters

bearing different substituents (F, Cl, Br, OMe, Me, naphthyl, thiophenyl) gave similar results and did not cause limitations in the parallel kinetic resolution. The enantiomeric excess of most of pyrrolidine products can be reached up to 99% *ee* under mild reaction conditions.

Notably, the importance of silicon-based bulky group on racemic MBH-derived silyl ethers on the PKR process is also supported by the investigation of substrate scope. For example, the use of racemic MBH-derived silyl ether **1f** ($MePh_2Si$-) led to the corresponding product **4z** with only 58:42 *dr*, while racemic MBH-derived silyl ether **1g** ($Ph_3Si$-) yielded the adduct **4aa** with only 87:13 *dr* (Scheme S1 of Supporting Information). In addition, the absolute configuration of the pyrrolidine product **4** was confirmed by X-ray analysis of **4s** (Figure 2)[12] and NMR analysis (See Supporting Information, nosy spectra of corresponding product **4e**) based on chiral MBH-derived silyl ether (*R*-configuration), and it was also supported indirectly by the absolute configuration of known product **3** because it has the same configuration at α-position of amino acid backbone. Notably, we also performed the present PKR procedure on the gram scale, and it was found that much better enantioselectivity of major isomer of **4h** was achieved under the optimized reaction conditions (97% *ee* versus 90% *ee*, see Scheme S1 of Supporting Information, eq. 3).




**Scheme 2**. Substrate scope for the parallel kinetic resolution: Asymmetric 1,3-dipolar [3+2] cycloaddition reaction and tandem conjugate addition-elimination reaction.

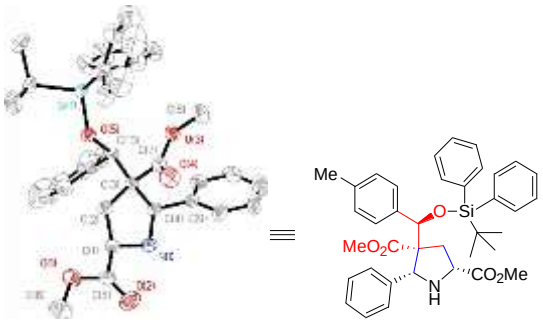



**Figure 2**. X-ray structure of **4s** (CCDC 1584134).

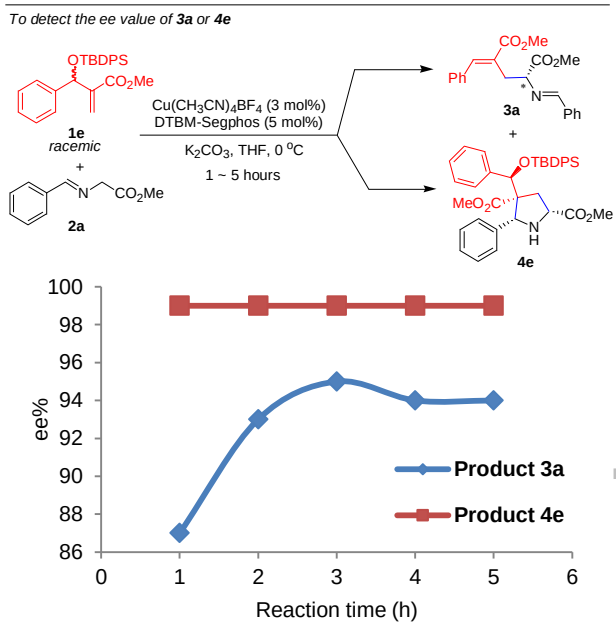



**Figure 3**. Relationship between the optical purity of the product **3a**/**4e** and reaction time (h).

Based on the reaction results of parallel kinetic resolution as well as the relationship between the optical purity of the product **3a**/**4e** and reaction time (Figure 3), we proposed the following reaction mechanism for the present parallel kinetic resolution (Figure 4). Although a full mechanistic process on the highly competitive and stepwise reaction that copper-catalyzed tandem conjugate addition-elimination reaction and cycloaddition occurred synchronously should await further studies, the initial coordination of the phosphine ligand with copper(I) to the formation of Cu-complex **A** (Figure S3 of ESI) resulted into the formation of a key copper-bound azomethine ylide by interaction with glycine aldimino esters.[9,12] A subsequent conjugate addition by attacking the carbon-carbon double bond of activated MBH-derived silyl ether **1** gave divergent

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process with the almost the same level of reaction rate, in which the transformation of catalyst-substrate complex B containing (*S*)-**1** would be possibly beneficial to undergo elimination of TBDPS -silyl ether group to give the desired enantioenriched glutamic acid derivatives **3** simultaneously. Because of high activity of 1,3-dipolarophile intermediate derived from (*R*)-**1**, the 1,3-dipolar [3+2] cycloaddition of racemic **1** and **2** to form the pyrrolidine product **4** would be sterically favorable process (Figure 4). Therefore, the observed formation of pyrrolidines **4** bearing four contiguous stereogenic centers can be explained by steric repulsion between the intermediate A and MBH-derived silyl ether from C through this stepwise mechanism, in which the substituent R/Ar of two substrates as well as TBDPSO group on the $sp^3$ carbon atom of MBH-derived silyl ether **1** would be an important factor to discriminate enantiomers (*R*)-**1** and (*S*)-**1** in this parallel kinetic resolution.

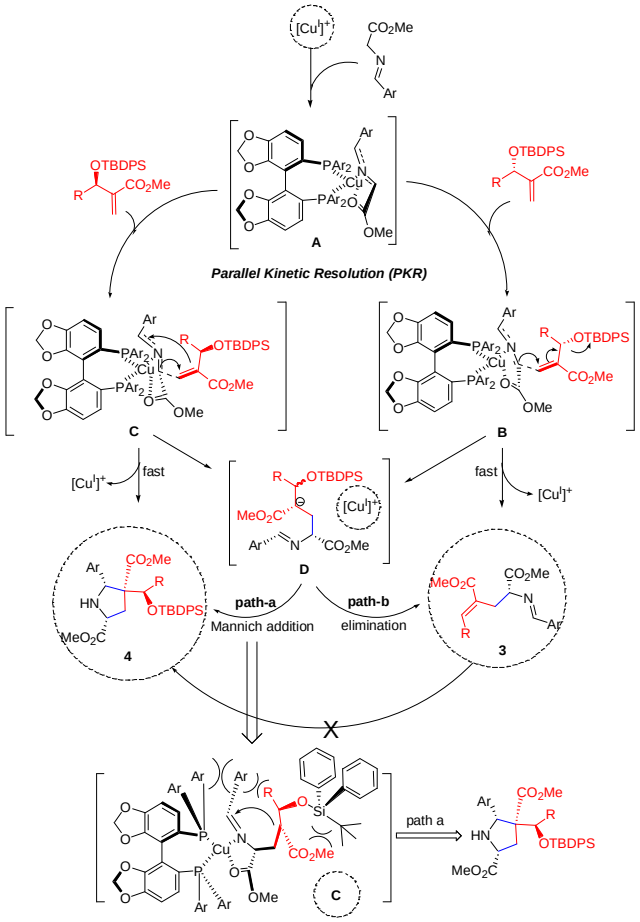


**Figure 4**. Plausible reaction mechanism for the parallel kinetic resolution based on copper-catalyzed 1,3-dipolar [3+2] cycloaddition and tandem conjugate addition-elimination reaction with the same substrates.

In summary, we have demonstrated that by applying the new strategy of silicon-based bulky group –tuned parallel kinetic resolution (PKR) to asymmetric 1,3-dipolar [3+2] cycloaddition reactions and tandem conjugate addition-elimination reaction, allowing for the efficient conversion of a racemic MBH adducts to two structurally different types of amino acid derivatives with high optical purity (up to 99% *ee*). This is an unprecedented and highly enantioselective 1,3-dipoalr addition-initiated chemodivergent PKR process that can be accomplished smoothly by using copper/DTBM-Segphos catalyst system. We believe that this PKR strategy reported in this work will be proved to be particularly useful for synthetic transformation of racemic materials.

**Experimental Section**

**General procedure for the copper-catalyzed PKR process: catalytic asymmetric cycloaddition and Michael addition of iminoesters with Morita-Baylis-Hillman -derived silyl ethers.** Under $N_2$ atmosphere, (*R*)-DTBM-SegPhos (11.8 mg, 0.01 mmol) and $Cu(CH_3CN)_4BF_4$ ( 1.9 mg, 0.006 mmol) were dissolved in 2 mL dry THF, and stirred at room temperature for about 0.5 h. Then iminoesters **2** (0.20 mmol) and $K_2CO_3$ (0.02 mmol) were added sequentially, the mixture was dropped to 0°C and then the TBDPS-protected Morita-Baylis-Hillman adducts **1** (0.20 mmol) was added. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. A portion of the residue was analyzed with $^1H$ NMR to determine the diastereomeric ratio. The crude was purified by column chromatography to give the corresponding known product **3** and new product **4**, which was then directly analyzed by HPLC to determine the enantiomeric excess. All the products **3** have been analysed by NMR, HRMS and chiral HPLC (see Supporting Information).

## Acknowledgements

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# Silicon-based Bulky Group–Tuned Parallel Kinetic Resolution in Copper-Catalyzed 1,3-Dipolar Additions

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