Organic LETTERS

Letter

pubs.acs.org/OrgLett

Asymmetric Synthesis of First Generation Molecular Motors

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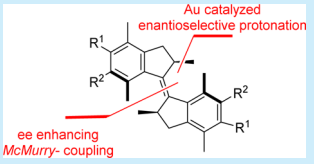
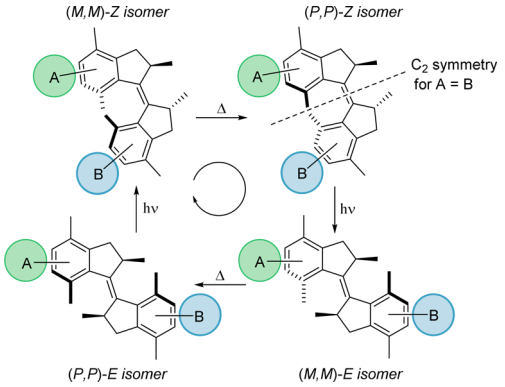
Supporting Information

ABSTRACT: A general enantioselective route to functionalized first generation molecular motors is described. An enantioselective protonation of the silyl enol ethers of indanones by a Au(I)BINAP complex sets the stage for a highly diastereoselective McMurry coupling as a second enhancement step for enantiomeric excess. In this way various functionalized overcrowded alkenes could be synthesized in good yields (up to 78%) and good to excellent enantiomeric excess (85% ee−>98% ee) values.



Photoswitchable catalysis is a highly promising approach toward the development of multifunctional, responsive, and multitasking catalysts.[1] Recently, our group reported the use of light-switchable chiral alkenes, i.e. molecular motors, as a dynamic molecular framework for responsive catalysis.[2] With this system, the stereochemical outcome of a carbon−sulfur bond-forming reaction could be controlled using light and temperature as external triggers to provide the racemic or either enantiomer of the chiral product with a single catalyst enantiomer. Using the molecular motor as a scaffold, both (pseudo)enantiomers of the *E*- and *Z*-isomer can be obtained selectively with light, thereby controlling the relative orientation of catalytically active groups A and B (Scheme 1). In our efforts

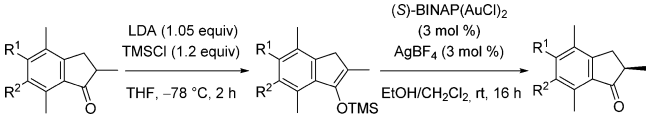
Scheme 1. Rotary Cycle of Molecular Motor



to improve the system and develop other light-addressable multifunctional catalysts, a practical problem was encountered. The chiral overcrowded alkenes, which are the key building blocks of these catalysts, could, until now, only be accessed in their enantiopure form via preparative HPLC, resolutions, or rather demanding auxiliary based synthetic routes.[3] For future applications of molecular motors in smart and responsive systems, it is crucial to have a short and enantioselective route to these chiral building blocks. To access these chiral compounds in a more efficient way, a protocol for the asymmetric synthesis was developed consisting of two stages. The first step is the asymmetric synthesis of various chiral indanones, which in the second stage can be dimerized using a diastereoselective reductive McMurry coupling mediated by titanium,[4] giving the desired overcrowded alkenes. In this letter, we report on the development of a short catalytic enantioselective synthesis of various functionalized molecular motors.

Enantioselective protonation is a very efficient way to access optically active substituted indanones.[5] It was shown by Toste et al.[6] that 2-methyl-1-indanone can be obtained in high enantiomeric excess by the Au(I) catalyzed asymmetric protonation of the corresponding silyl enol ether. With a slight modification of the methodology by Toste, the substrate scope was expanded to various substituted indanones (Table 1). The

Table 1. Enantioselective Indanone Protonation



entry	R^1	R^2	product	yield (%)[a]	ee (%)[b]
1	H	H	**1**	85	81
2	H	Br	**2**	86	97
3	Br	H	**3**	88	94
4	H	OTBS	**4**	82	78
5	OTBS	H	**5**	81	7
6	OMe	H	**6**	84	4
7	OBz	H	**7**	86	87
8	H	OBz	**8**	86	98
9	OTroc	H	**9**	27	97
10	H	OTroc	**10**	27	98

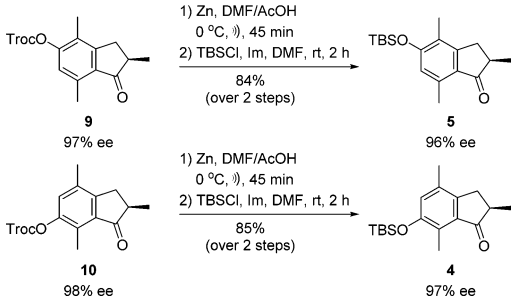
[a]Isolated yields over two steps. [b]Determined by chiral-HPLC or SFC.

Received: July 3, 2014
Published: July 31, 2014

   dx.doi.org/10.1021/ol501925f | *Org. Lett.* 2014, 16, 4220−4223

enantioselective protonation of the silyl enol ethers derived from the corresponding racemic indanones gives the desired ketones in good yields (up to 88% over two steps) and excellent enantiomeric purity (up to 97% ee). It was found that the electronic nature of the substituent at position 5 or 6 of the indanone has a crucial influence on the enantioselectivity. The asymmetric protonation of the silyl enol ethers of indanones with bromo-substituents at the 5- or 6-position provide 97% ee (entry 2) and 94% ee (entry 3), respectively, giving a significantly higher enrichment than observed for unsubstituted enol ether, which gives 81% ee (entry 1). Particularly important for the functional motors are protected chiral indanones bearing hydroxyl groups. However, in the case of indanones with siloxy- and methoxy-substituents at the 5- and especially the 6-position (entries 4−6) the enantiomeric excesses were much lower (4−78% ee), probably due to a faster uncatalyzed background ethanolysis of the silyl enol ether during the reaction. By changing to a more electron-withdrawing protective group on the phenolic group, like benzoate (entries 7 and 8) or carbonate (entries 9 and 10), high stereoselectivity (up to 98% ee) could be regained. The low yields in the case of the 2,2,2-trichloro-ethoxycarbonyl (Troc) protective group (entries 9 and 10) derives from unselective deprotonation during the silyl enol formation causing partial deprotection. Since the benzoate and sensitive Troc protected indanones are not tolerated in the following McMurry coupling, a transformation to the corresponding silylether was necessary. Unfortunately all attempts to cleave the benzoic ester via hydrolysis, transesterification, or reduction led to racemization or decomposition. To reduce the degree of racemization in the case of the Troc protected indanones **9** and **10** to a minimum, a sonication assisted deprotection using Zn/AcOH was applied to provide, after silylation, the ketone **4** and **5** in both cases in good yields (85% and 84% over two steps), with almost full conservation of the enantiomeric excess (Scheme 2).[7]

Scheme 2. Protective Group Manipulation of the Troc-indanones 9 and 10



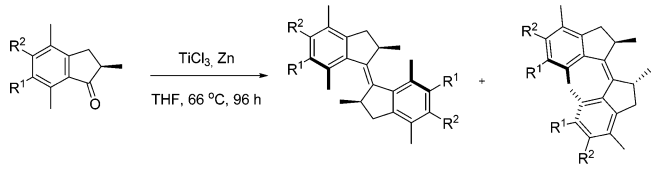
With the enantioenriched ketones in hand, the next step was the construction of the sterically hindered double bond in the overcrowded alkenes. It was important to find a condition for the McMurry coupling which shows complete retention of configuration and does not racemize the configurationally extremely labile α stereocenter of the carbonyl group. To achieve this goal various conditions were screened, to find the perfect combination of the titanium source and reductant. Unfortunately the common method, employing $TiCl_4$ as the titanium source and zinc as the reductant, gave unreproducible results with regard to the degree of racemization of the ketone during the reaction.[3b] These findings indicate that the high Lewis acidity of $TiCl_4$ is responsible for the racemization. Therefore, we decided to use the less Lewis acidic $TiCl_3$ as the titanium source, which was anticipated to give the coupled product without racemization.[8] Using a combination of $TiCl_3$ and $LiAlH_4$ as the reductant, the desired product **11** was obtained without racemization.[8] The desired product **11** was obtained without racemization in 38% yield with an *E*/*Z* ratio of 40/60 in the case of ketone **2**.[8] More surprisingly, the product was obtained with an enantiomeric excess of >98% ee (for the *E* isomer), starting from 89% ee for ketone **2**. An amplification of enantiomeric purity in the McMurry coupling has, as far as we know, not been reported in the literature. A rationalization for this observation is given further on. Unfortunately the formation of a mono- and nonhalogenated product as side products was observed, which were inseparable from the desired product **11**. The combination of $TiCl_3$ and $LiAlH_4$ results in the formation of a reactive titanium(II) hydride species,[9] which is assumed to be the cause for the significant dehalogenation of product **11**.

To avoid the formation of dehalogenated side products, the combination of $TiCl_3$ and zinc as the reductant was chosen.[10] These conditions are much milder than those using $LiAlH_4$ as the reductant, which indeed prevents the formation of dehalogenated side products. Also by using zinc as the reductant the reaction showed similar chiral amplification; i.e., the enantiomeric purity of the product is enhanced compared to that of the starting material. Moreover, the yield of the McMurry coupling is significantly improved using zinc compared to $LiAlH_4$ (92% vs 38%, Table 2). However, the enhancement is smaller in comparison to the case where $LiAlH_4$ is employed as the reductant. With these conditions no dehalogenation was observed and the substrate scope for overcrowded alkene formation and the generality of this enhancement of enantiomeric excess were explored. By varying the enantiopurity of the starting material (entries 1−3) and the nature of the substituents (entries 4−7), it could be shown that the amplification was observed in all cases (entries 1−7). The 5-bromo substituted ketones **2** formed the desired McMurry product **1** in 85% yield with an *E*/*Z* ratio of 50/50 and >98% ee, starting from 97% ee for the ketone **2** (entry 1, Table 2). The 6-bromo indanone **3** gives coupling product **12** in 89% yield, with an *E*/*Z* ratio of 40/60 and 98% ee. Using the unsubstituted indanone **1** it was shown that the enhancement on ee differs for the *E*- and *Z*-isomers. Whereas the *Z*-isomer results with 85% ee lower excess than the *E*-isomer with 91% ee, the increase is nevertheless still significant considering an enantiopurity of 81% ee for the starting material **1**. The ketone **4** bearing a TBS-group at the 6-position shows only a slight increase in ee (entry 6) which is distinct from the 5-substituted overcrowded alkene **15**, the latter reaching >98% ee for both *E*- and *Z*-isomers. In all cases an enhancement of the enantiomeric excess was observed, which is more pronounced in the case of $LiAlH_4$ as the reductant (*vide supra*, Scheme 3). It is noteworthy that the formation of the undesired (*R*,*S*)-diastereomer of the overcrowded alkenes (i.e., (*R*,*S*)-**14**, Scheme 4) was never observed in any McMurry coupling of these or similar overcrowded alkenes. Furthermore, this indicates that the increase in enantiomeric excess is not due to formation and separation of diastereoisomers. The highly diastereoselective step seems to be the pinacol coupling, respectively, the alkene formation.

As it was shown in the case of the McMurry reaction with $TiCl_3$/Zn that, for the reduction of the titanium(III)chloride by zinc, a prior complexation of the ketone to Ti(III) is essential,[10]

dx.doi.org/10.1021/ol501925f | *Org. Lett.* 2014, 16, 4220−4223

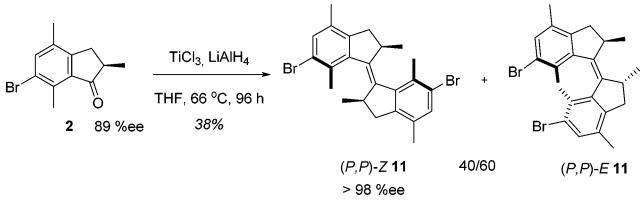
Table 2. Diastereoselective McMurry Coupling Using Zn as Reductant



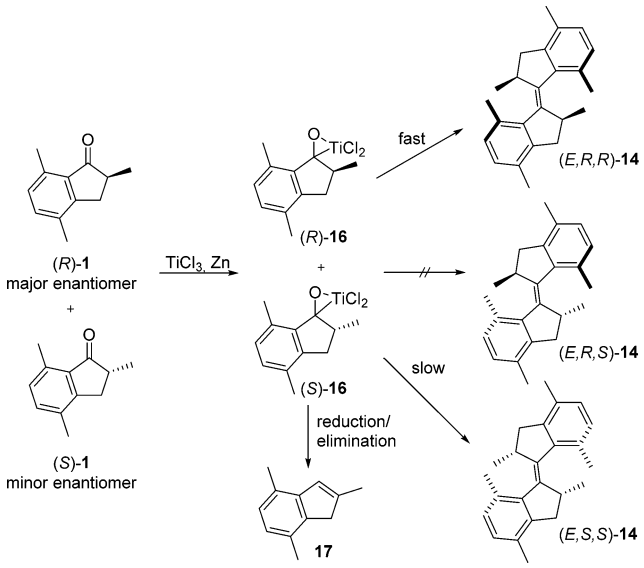
entry	R^1	R^2	ee of ketone (% ee)[a]	yield (%)[b]	product	E/Z[c]	ee (% ee)[d]
1	H	Br (**2**)	97	85	**11**	50/50	99
2	H	Br (**2**)	94	82	**11**	45/55	97
3	H	Br (**2**)	89	75	**11**	50/50	93
4	Br	H (**3**)	94	89	**12**	40/60	98
5	H	H (**1**)	81	86	**13**	25/75	91
							Z: 85
6	H	OTBS (**4**)	97	92	**14**	50/50	99[e]
							Z: 99[e]
7	OTBS	H (**5**)	96	90	**15**	44/56	97[e]

[a]Determined by chiral-HPLC or SFC. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Enantiomeric excess of *E*-isomer if not stated otherwise, determined by chiral-HPLC or SFC. [e]Determined after TBS deprotection.

Scheme 3. McMurry Coupling Using $LiAlH_4$ as Reductant



Scheme 4. Proposed Mechanism of the Amplification



leading to the irreversible formation of a low-valent titanium(II) species (i.e., **16**), with equal rates for both enantiomers. This is consistent with the observation that the enantiomeric ratio of the starting material (**1**) stays constant during the reaction. This results in a much lower concentration of the minor (*S*)-titanium(II) complex (*S*)-**16** compared to the major enantiomer (*R*)-**16**, which relates to a much lower reaction rate of the minor enantiomer in the highly diastereoselective dimerization, because of the square dependency of the concentration. This "pseudo"-dilution of the titanium(II) complex of the minor enantiomer is assumed to be the cause of the observed enhancement of enantiomeric excess within the reaction.

In other words due to the much lower concentration, the minor (*S*)-complex will show a much longer reaction time for the dimerization, which increases the probability for reductive side reactions, such as the one leading to the observed side product **17**. The combination of the proposed dilution effect of the minor enantiomer, the diastereoselective dimerization, and the reductive side reactions upon prolonged reaction time explains why for a stronger reductant such as $LiAlH_4$ compared to Zn the yield is lower (38% vs 92%), but the enhancement of ee is higher. In the case of a strong reductant such as $LiAlH_4$, the reductive side reaction is faster; therefore, the effect of the concentration-dependency of the dimerization becomes more pronounced. The enantiomer excess increases from 89% ee to >98% ee for $LiAlH_4$ (Scheme 3) compared to 94% ee in the case of the use of zinc as the reductant (entry 3, Table 2). However, the side reactions of the major enantiomer are also increased, thereby lowering the overall yield.

In summary, an asymmetric catalytic synthesis of functionalized first generation molecular motors has been developed in high yields (up to 78% over three steps) and excellent enantiomeric excesses (up to >98% ee). The key features of this approach are the use of the catalytic enantioselective protonation of silyl enol ethers by a cationic Au(I)BINAP complex giving access to the enantiomeric enriched ketones (81% ee −98% ee) followed by a highly diastereoselective McMurry coupling with an ee amplification step yielding overcrowded alkenes with up to >98% ee. This is, to the best of our knowledge, the first example of amplification of chirality in the McMurry reaction. This asymmetric synthetic route sets the stage for further application of chiral overcrowded alkenes in smart materials or photoswitchable catalysis, which are ongoing research topics in our group.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization of all compounds. NMR, HRMS, HPLC, and SFC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol501925f | *Org. Lett.* 2014, 16, 4220−4223

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the European Research Council (Advanced Investigator Grant, No. 227897 to B.L.F.); The Netherlands Organization for Scientific Research (NWO-CW); funding from the Ministry of Education, Culture and Science (Gravity program 024.001.035); The Royal Netherlands Academy of Arts and Sciences (KNAW); and NRSC-catalysis are gratefully acknowledged. Thomas M. Neubauer acknowledges the DAAD for funding.

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